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(71)Applicant : API CO LTD
YAMADA BEE FARM

(72)Inventor : OGAWA KAZUAKI
YAMADA HIDEO
TOKUNAGA KATSUHIKO
MARUYAMA HIROE
SAKAMOTO TAKASHI
MISHIMA SATOSHI

(54) PROPOLIS COMPOSITION AND ITS GRANULAR PREPARATION

(57)Abstract:
PROBLEM TO BE SOLVED: To provide a propolis composition constituted so as to exhibit high efficacy as a healthy food and a cosmetic material, and further to provide its granular preparation.
SOLUTION: This propolis composition contains the propolis extracted with a hydrophilic organic solvent, the propolis extracted with water, and the propolis extracted by supercritical extraction, regulated so that the propolis extracted with the hydrophilic organic solvent will be 1-20 pts.wt. and the propolis extracted with the water will be 0.5-6 pts.wt. based on 1 pts.wt. propolis extracted by the supercritical extraction. The propolis extracted with the water and the propolis extracted by the supercritical extruction are preferably the ones extracted from a residue after extraction of an original lump of the propolis with the hydrophilic organic solvent. The propolis composition is preferably constituted of a powder of the extract of the propolis extracted with the hydrophilic organic solvent, a powder of the extract of the propolis extracted with the water, and a powder of the extract of the propolis extracted by supercritical extruction. The granular preparation of the propolis composition contains the propolis composition, and contains the propolis extracted with the hydrophilic organic solvent, the propolis extracted with the water, and the propolis extracted by the supercritical extruction.

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CLAIMS

[Claim(s)]
[Claim 1] The propolis constituent which is a propolis constituent containing hydrophilic organic solvent extract propolis, water extract propolis, and supercritical extraction propolis, and is characterized by carrying out 0.5-6 weight section content of 1 - 20 weight section and the water extract propolis for hydrophilic organic solvent extract propolis to the supercritical extraction propolis 1 weight section.
[Claim 2] At least one sort chosen from said water extract propolis and supercritical extraction propolis is a propolis constituent according to claim 1 characterized by being extracted from the residue after a hydrophilic organic solvent extracts a propolis original lump.
[Claim 3] The propolis constituent according to claim 1 or 2 characterized by exceeding 10 weight sections for hydrophilic organic solvent extract propolis, and carrying out 1-5 weight section content of the water extract propolis below 18 weight sections to the supercritical extraction propolis 1 weight section.
[Claim 4] A propolis constituent given in either of claim 1 to claims 3 characterized by containing the hydrophilic organic solvent extract powder which carried out disintegration of said hydrophilic organic solvent extract propolis, the water extract powder which carried out disintegration of said water extract propolis, and the supercritical extraction object powder which carried out disintegration of said supercritical extraction propolis.
[Claim 5] Propolis constituent granulation pharmaceutical preparation characterized by containing the hydrophilic organic solvent extract granulation which is the propolis constituent granulation pharmaceutical preparation which contains the propolis constituent of a publication in either of claim 1 to claims 4, and corned said hydrophilic organic solvent extract propolis to granularity, the water extract granulation which corned said water extract propolis to granularity, and the supercritical extraction object granulation which corned said supercritical extraction propolis to granularity.

[Translation done.]

JAPANESE [JP,2003-061593,A]

CLAIMS DETAILED DESCRIPTION TECHNICAL FIELD PRIOR ART EFFECT OF THE INVENTION TECHNICAL PROBLEM MEANS OPERATION EXAMPLE

[Translation done.]

* NOTICES *

1.This document has been translated by computer. So the translation may not reflect the original precisely.
2.**** shows the word which can not be translated.
3.In the drawings, any words are not translated.

DETAILED DESCRIPTION

[Detailed Description of the Invention]
[0001]
[Field of the Invention] This invention relates to the propolis constituent used as health food pharmaceutical preparation, cosmetics pharmaceutical preparation, etc., and the propolis constituent granulation pharmaceutical preparation containing that constituent.
[0002]
[Description of the Prior Art] propolis (propolis original lump) -- a bee -- it is the matter of the shape of the shape of resin which is also called tar and constitutes **** of the blow hole of an Apis mellifrera, and wax. A honeybee is sap and the plant body which have been extracted from surrounding vegetation, beeswax and pollen are often mixed, and generally this propolis presents blackish brown thru/or dark brown, and contains various components.
[0003] Although this propolis had been used as a raw material of drugs or health food in Europe for many years, it came to be used for many products as a raw material of health food or cosmetics also in Japan in recent years. As main bioactive of propolis, active oxygen elimination ability and an immunity activation operation are known, and the efficacy as a raw material of health food is supported. Moreover, quenching, the analgesic action, the antiallergic operation, and the antibacterial action to the disease germ of the large range are also known. It is reported at an institute especially that there are remarkable anticancer and antitumor action, and since the discovery report of two or more new cancericidal material was carried out out of the component, the efficacy which was excellent in propolis will attract attention of a world suddenly.
[0004] TERUPE ** with a still lower polarity, such as flavonoids from an organic-acid compound with a polarity high as a chemical entity contained in this propolis, and polyphenol, -- the id -- very many compounds, such as a kind, are checked. It is thought that the bioactive which the bioactive of these matter acts intricately, has it and was excellent in propolis is formed.
[0005] Since the propolis original lump is very difficult, it is [taking in in the condition as it is] common to be taken in as an extract extracted with a hydrophilic organic solvent or water, such as ethanol. Various physiological active substances contain in the hydrophilic organic solvent extract or water extract of this propolis, and various products which used that pharmacological action in the health food field are marketed. Moreover, in JP,2000-325032,A, it is indicated by alcoholic extract propolis by adding and mixing water extract propolis gradually about the propolis product which carried out precipitation filtration and removed the resinous principle peculiar to alcoholic extract propolis. And this propolis product supposes that it is suitable for drink as compared with the propolis extract extracted with the independent solvent (alcohol or water) in the synergistic effect of each component being expectable while conquering the difficulty which each of alcoholic extract propolis and water extract propolis has.
[0006]
[Problem(s) to be Solved by the Invention] However, with the propolis product containing said alcoholic conventional extract propolis and water extract propolis, only the component meltable to alcohol among the components in a propolis original lump and the component meltable in water were contained, but many active principles are lost by moreover removing a resinous principle in a precipitation filtration process, and a part of propolis active principle was able to be taken in. For this reason, compared with the bioactive synergistic effect by many active principles when taking in a propolis original lump the whole ****, it was remarkable and said synergistic effect was low.
[0007] This invention is made paying attention to the trouble which exists in the above conventional techniques. The place made into the object is to offer the propolis constituent constituted so that efficacy high as health food and a cosmetics raw material could be demonstrated, and its granulation pharmaceutical preparation.
[0008]
[Means for Solving the Problem] In order to attain the above-mentioned object, the propolis constituent of invention according to claim 1 is a propolis constituent containing hydrophilic organic solvent extract propolis, water extract propolis, and supercritical extraction propolis, and is characterized by carrying out 0.5-6 weight section content of 1 - 20 weight section and the water extract propolis for hydrophilic organic solvent extract propolis to the supercritical extraction propolis 1 weight section.
[0009] At least one sort as which the propolis constituent of invention according to claim 2 is chosen from said water extract propolis and supercritical extraction propolis in invention according to claim 1 is characterized by being extracted from the residue after a hydrophilic organic solvent extracts a propolis original lump.
[0010] The propolis constituent of invention according to claim 3 is characterized by exceeding 10 weight sections for hydrophilic organic solvent extract propolis, and carrying out 1-5 weight section content of the water extract propolis below 18 weight sections to the supercritical extraction propolis 1 weight section, in invention according to claim 1 or 2.
[0011] The propolis constituent of invention according to claim 4 is characterized by containing the hydrophilic organic solvent extract powder which carried out disintegration of said hydrophilic organic solvent extract propolis to either of claim 1 to claims 3 in invention of a publication, the water extract powder which carried out disintegration of said water extract propolis, and the supercritical extraction object powder which carried out disintegration of said supercritical extraction propolis.
[0012] The propolis constituent granulation pharmaceutical preparation of invention according to claim 5 The hydrophilic organic solvent extract granulation which is the propolis constituent granulation pharmaceutical preparation which contains the propolis constituent of a publication in either of claim 1 to claims 4, and corned said hydrophilic organic solvent extract propolis to granularity. It is characterized by containing the water extract granulation which corned said water extract propolis to granularity, and the supercritical extraction object granulation which corned said supercritical extraction propolis to granularity.

[0013]
[Embodiment of the Invention] Hereafter, the operation gestalt which materialized this invention is explained to a detail. The propolis constituent of an operation gestalt contains hydrophilic organic solvent extract propolis (it is hereafter indicated as a hydrophilic organic solvent extract), water extract propolis (it is hereafter indicated as a water extract), and supercritical extraction propolis (it is hereafter indicated as a supercritical extraction object). the gestalt of pharmaceutical preparation of versatility [constituent / this / propolis], such as health food pharmaceutical preparation and cosmetics pharmaceutical preparation, -- taking orally -- or dermal administration is carried out and it is used. A very high health promotion operation and the cosmetics effectiveness are demonstrated according to the synergistic effect of the active principle contained in three kinds of extracts by the extract approach that these propolis constituents differ. Said health promotion operation and the cosmetics effectiveness are presumed and checked by carrying out the measurement comparison of the radical prehension acceleration activity used as the index of edema control activity, hyaluronidase inhibition activity, leucocyte phagocytosis acceleration activity, and active oxygen elimination ability.
[0014] Three kinds of respectively separate propolis original lumps are prepared, and the start raw material (it is hereafter indicated as a propolis raw material) for extracting each extract can be used for three kinds of extract operation. However, when the workability of an extract process and the recovery (profitability) of an active principle are taken into consideration, it is desirable to constitute so that two or more kinds of extract operation may extract a propolis original lump. That is, after a hydrophilic organic solvent extracts a propolis original lump first, a water extract or supercritical extraction may be presented with the residue (residue of insolubility [organic solvent / hydrophilic]), and a hydrophilic organic solvent extract or a water extract may be presented with the residue after carrying out supercritical extraction to reverse.
[0015] the residue (residue) after performing a hydrophilic organic solvent extract previously most preferably using a propolis original lump -- a water extract -- or it is good to constitute so that supercritical extraction may be carried out. Since the hydrophobic component located in the boundary region which may be extracted with the hydrophilic component located in the boundary region which may be extracted with water and a hydrophilic organic solvent at this time or supercritical extraction, and a hydrophilic organic solvent overlaps into a propolis constituent and does not contain, it is easy to reduce the depressor effect over the health promotion effectiveness etc. That is, when said hydrophilic component or a hydrophobic component is taken in so much at once, there is work which controls health promotion on the contrary. Moreover, since permeability is good in the operation of a hydrophilic organic solvent, the residue after presenting a hydrophilic organic solvent extract previously can raise easily the yield in a subsequent water extract or supercritical extraction.
[0016] In addition, although anything of places of production, such as Brazil, China, Japan, the U.S., and Europe, of said propolis original lump is usable, it is desirable especially to use the product from Brazil with high extract yield in a water extract.
[0017] Although a hydrophilic organic solvent extract is obtained by extracting a meltable component to the hydrophilic organic solvent in a propolis raw material, using a hydrophilic organic solvent or its water diluent as an extracting solvent, it is desirable to use ethanol for manufacture of the constituent as health food as a hydrophilic organic solvent. Various active principles, such as flavonoids, polyphenol, organic acids, and Tell ** NOIDO, are contained in this hydrophilic organic solvent extract, and a health promotion operation of an active oxygen elimination operation, an immunity activation operation, quenching, an anticancer operation, etc. is demonstrated.
[0018] Considering that they carry out taking orally, using the property and propolis constituent of a solvent as food, said hydrophilic organic solvent has the most desirable ethanol, although they can use it, ketones which have the property dissolved in water, such as an acetone besides lower alcohol, such as ethanol, a methanol, and isopropanol, and a methyl ethyl ketone, choosing it suitably. the time of using ethanol as a hydrophilic organic solvent -- the concentration -- desirable -- 60 to 100 capacity % -- it is 80 to 100 capacity % more preferably. When this concentration is under 60 capacity %, it is a ratio suitable for the configuration of this operation gestalt, and an active principle meltable to ethanol cannot be extracted efficiently. the amount of the ethanol used -- a propolis raw material -- receiving -- desirable -- the amount of one to 20 times -- more -- desirable -- the amount of two to 10 times -- it is the amount of three to 8 times still more preferably. When this amount used is under the amount of 1 time, the yield of an active principle falls. Conversely, in exceeding an amount 20 times, equipment not only becomes large superfluously, but starting workability falls [time amount] to processes, such as concentration, remarkably.
[0019] The temperature 10-30 degrees C near ordinary temperature is sufficient as extract temperature, and it is good to perform extract operation for 24 hours or more, stirring at the extract temperature. In addition, when said extract temperature is less than 10 degrees C, the yield of an active principle falls. Conversely, in exceeding 30 degrees C, the filterability after an extract worsens and workability falls. And after fully extracting an active principle by the above-mentioned extraction condition, hydrophilic organic solvent extract liquid is obtained by performing filter paper filtration or diatomaceous earth filtration. A hydrophilic organic solvent extract is obtained by evaporating and drying the solvent of this hydrophilic organic solvent extract liquid. Since powder physical properties are inferior, after [brown] accepting the need and diluting and condensing said hydrophilic organic solvent extract liquid, it dries, and excipients, such as a lactose and a dextrin, are added and it is [this hydrophilic organic solvent extract carries out disintegration and] good [it is, it carries out and is a dark-brown resin-like solid-state, if this is ground, pure hydrophilic organic solvent extract powder will be obtained but] also as hydrophilic organic solvent extract powder.
[0020] A water extract is obtained by extracting a meltable component in the water in a propolis raw material, using water as an extracting solvent. Various active principles, such as organic acids, polysaccharide, and protein, are contained in this water extract, and a health promotion operation of an antioxidation operation, a radical prehension acceleration operation, hyaluronidase inhibition activity, an anticancer operation, etc. is demonstrated. the amount of the extracting solvent used -- a propolis raw material -- receiving -- desirable -- the amount of one to 20 times -- more -- desirable -- the amount of two to 15 times -- it is the amount of five to 12 times still more preferably. When the amount of this extracting solvent used is under the amount of 1 time, the yield of an active principle falls. Conversely, in exceeding an amount 20 times, starting workability falls [time amount] to processes, such as concentration, remarkably.
[0021] 20-90 degrees C of 30-80 degrees C of extract temperature are 40-60 degrees C still more preferably more preferably. When this extract temperature is less than 20 degrees C, it not only causes deterioration of quality, but an extract process takes a long time and the yield of an active principle falls. Conversely, when exceeding 90 degrees C, it is expected that the denaturation of an active principle takes place and the synergistic effect falls. Moreover, although extract time amount is based also on the amount of the extracting solvent used, in order to extract sufficient quantity of an active principle, it is desirable to apply for 2 hours or more and to extract.
[0022] And after fully extracting an active principle by the above-mentioned extraction condition, water extract liquid is obtained

by performing filter paper filtration or diatomaceous earth filtration. Furthermore, if it freeze-dries if needed after condensing this water extract liquid, pure water extract freeze-drying powder will be obtained. In order to obtain powder with still more sufficient physical properties, it is good also as water extract freeze-drying powder which freeze-dried after adding excipients, such as a lactose and a dextrin, in the aforementioned water extract liquid, and was excellent in the powder property. Moreover, even if it adds excipients, such as a lactose and a dextrin, to the aforementioned pure water extract freeze-drying powder, water extract freeze-drying powder with a sufficient powder property (it is hereafter indicated as water extract powder) is obtained.
[0023] A supercritical extraction object extracts a predetermined component from a propolis raw material by contacting the supercritical fluid and the propolis raw material which changed supercritical fluid into the supercritical condition under the conditions more than critical temperature and more than the critical pressure using well-known supercritical-fluid-extraction equipment. When using a carbon dioxide as supercritical fluid, the carbon dioxide which changed into the supercritical fluid condition as more than the critical temperature of 31.1 degrees C and more than the critical pressure of 72.8 atmospheric pressures (7.4MPa) extracts a propolis raw material. Flavonoids, Tell ** NOIDO, other hydrophobic physiological active substances, etc. are contained in the supercritical extraction object using this carbon dioxide, and demonstrating a health promotion operation of hyaluronidase inhibition activity, an anticancer operation, edema depressant action, etc. is checked.
[0024] Although ethane, a propane, a carbon dioxide, nitrous oxide, etc. are usable, as for said supercritical fluid, it is most desirable to use a carbon dioxide. this carbon dioxide suits the compound for an extract that a polarity is lower than ethanol in a top with the critical temperature near ordinary temperature — it has physical and chemical property. Since the physical properties in an extract process are not only excellent in this way, but a carbon dioxide does not affect the taste of a supercritical extraction product by tasteless and no odor, as supercritical fluid used for this operation gestalt, its carbon dioxide is the most desirable.
[0025] In order that supercritical fluid may use a consistency and the property in which solubility changes a lot, to few temperature gradients and a pressure differential [near the critical point], the suitable vertical width of face for the temperature and the pressure of processing is required for actuation in supercritical fluid extraction. 32-80 degrees C of operating temperature in the case of using a carbon dioxide are 32-50 degrees C more preferably. Moreover, the actuation pressure is 73 to 400 atmospheric pressure (7.4-40.5MPa) more preferably 73 to 500 atmospheric pressure (7.4-50.7MPa). 1-10kg (the rate of flow) /of flow rates of the carbon dioxide as supercritical fluid is [hour] 3-7kg/hour more preferably to 1kg of propolis raw materials. Although the processing time changes with the amounts and conditions of a propolis raw material, it can be suitably determined from a test or a processing track record by checking the time amount which an extract completes.
[0026] And the description of the supercritical extraction object of the propolis extracted by the above-mentioned extraction condition changes also with the elapsed time of an extract. Although many are pastes-like, a part may be obtained as powder thru/or a massive solid-state. When using ethanol as an entrainer, it becomes liquefied including ethanol. The carbon dioxide which the ethanol by which it is contained in extraction feed immediately after an extract, the ethanol as an entrainer, etc. were contained, and also the supercritical extraction object solidified by adiabatic expansion is contained. Since it is obtained as an uneven extract with the presentation which furthermore changes with extract elapsed time, after removing ethanol and a carbon dioxide and considering as a solid supercritical extraction object, stirring to homogeneity, if it grinds, it will become pure supercritical extraction object powder. In order to give a further more good powder property, it is good also as supercritical extraction object powder which added and carried out disintegration of the excipients, such as a lactose and a dextrin, to the supercritical extraction object if needed.
[0027] the blending ratio of coal of the hydrophilic organic solvent extract in the propolis constituent of this operation gestalt — the supercritical extraction object 1 weight section — receiving — desirable — 1 - 20 weight section — 10 weight sections are exceeded more preferably and they are below 18 weight sections. To the supercritical extraction object 1 weight section, when the blending ratio of coal of a hydrophilic organic solvent extract is under 1 weight section, the sufficient efficacy and the effectiveness as health food or cosmetics pharmaceutical preparation cannot be demonstrated. Conversely, when the blending ratio of coal of a hydrophilic organic solvent extract exceeds 20 weight sections to the supercritical extraction object 1 weight section, since the content of the supercritical extraction object to a water extract falls relatively, the synergistic effect of these water extract and a supercritical extraction object is not fully demonstrated.
[0028] the blending ratio of coal of the water extract in the propolis constituent of this operation gestalt — the supercritical extraction object 1 weight section — receiving — desirable — 0.5 - 6 weight section — it is 1 - 5 weight section more preferably. To the supercritical extraction object 1 weight section, when the blending ratio of coal of a water extract is under the 0.5 weight section, the sufficient efficacy and the effectiveness as health food or cosmetics pharmaceutical preparation cannot be demonstrated. Conversely, when the blending ratio of coal of a water extract exceeds 6 weight sections to the supercritical extraction object 1 weight section, since the content of the supercritical extraction object to a hydrophilic organic solvent extract falls relatively, the synergistic effect of these hydrophilic-properties organic solvent extract and a supercritical extraction object is not fully demonstrated.
[0029] the propolis constituent constituted as mentioned above — as health food pharmaceutical preparation, cosmetics pharmaceutical preparation, etc. — taking orally — or dermal administration is carried out and it is used. In this propolis constituent, within limits which do not spoil the health promotion effectiveness of the above-mentioned active principle in that case For example, plumping agents, such as excipients, such as a dextrin, cyclodextrin, and a lactose, and a sodium hydrogencarbonate, Brighteners, such as a cull navarho, a shellac, and yellow bees wax, a pectin carboxymethyl cellulose, Gelling agents, such as agar and starch, an alginic acid, carrageenan, xanthan gum, Thickeners, such as chitosan, sugar, honey, a liquorice extract, a stevia, saccharin sodium, Sweetening agents, such as an oligosaccharide, erythritol, a starch syrup, and isomerized sugar, a quillaja extract, Emulsifiers, such as lecithin, a glycerol, a glycerine fatty acid ester, and an soybean saponin, pH regulators, such as coloring matter, such as flavorings, such as cinnamon essential oil, jasmine essential oil, rosemary essential oil, and lime essential oil, a caramel, a red cabbage, a gardenia, nonuniformity SAKIIMO, a grape, and curcmae rhizoma, a lactic acid, a lactate, a citric acid, a malic acid, and a sodium carbonate, may be added.
[0030] As health food pharmaceutical preparation, by adding the above-mentioned propolis constituent in a food raw material, a drink article raw material, or a drugs raw material, it is processed into configurations, such as the shape of the shape of powder, a liquid, granularity, a tablet, and a capsule, and a stick, and is used as health food, a health drink, or quasi drugs. It is used as quasi drugs, being blended with soap, gear-tooth polishing powder, etc. As cosmetics pharmaceutical preparation, by adding the above-mentioned propolis constituent for a food raw material, a drink article raw material, or a cosmetics raw material, it is processed into the shape of a liquid, a milk liquid, and a half-solid, and the configuration of powdered **, and is used as cosmetics food, a cosmetics drink, or cosmetics. According to the class of makeup, as for said cosmetics, alcohols, a fats-and-oils surfactant,

purified water, etc. are added suitably.
[0031] On the other hand, it is processed into many gestalten, such as a tablet, a capsule, granulation, powder, syrups, and drinkable preparations, when using this propolis constituent as an oral agent. When processing it into a tablet and a capsule, a binder, an excipient, a plumping agent, a brightener, a sweetening agent, a flavor agent, etc. are added suitably. A tablet can also be covered with a shellac or sugar. Moreover, the above-mentioned ingredient can be made to contain liquid support, such as fats and oils, further in the case of a capsule. On the other hand, when using as a parenteral agent, it is used with the gestalt of external preparations, such as an ointment, cream pharmaceuticals, and liquor, carrying out dermal administration. As a basis of these external preparations, vaseline, paraffin, fats and oils, lanolin, macro gall, etc. are used suitably, and can consider as an ointment, cream pharmaceuticals, etc. by the usual approach.
[0032] It is desirable to consider as granularity granulation pharmaceutical preparation with big particle diameter on the other hand, since possibility that the component in a propolis constituent will join during preservation according to moisture absorption etc. is high when the above-mentioned propolis constituent is made into the shape of powder and powder of especially minute particle diameter.
[0033] in considering this propolis constituent as granulation pharmaceutical preparation, after mixing three kinds of extracts — disintegration -- carrying out — granulator — a law -- according to a method, it can fabricate to granularity, and can consider as granulation pharmaceutical preparation. Or mixing three kinds of extracts by which disintegration was carried out using granulator, it can corn to granularity and can also consider as granulation pharmaceutical preparation. Or it is also possible to consider as propolis constituent granulation pharmaceutical preparation by mixing spraying directly the liquid (liquefied propolis constituent) which mixed three kinds of extracts on the front face of the raw material granulation beforehand corned by granularity by purified sucrose, corn starch, etc., or making three kinds of extracts by which disintegration was carried out adhere to it through a sizing agent using coating granulator, and making it dry after that.
[0034] However, since possibility that problems, such as separation, will arise according to a difference of the properties (strength of lipophilicity etc.) of each extract by the manufacture approach of the above-mentioned granulation pharmaceutical preparation at the time of mixing or preservation is high, after making it granularity for every extract, considering as granulation pharmaceutical preparation is most desirable by mixing by the predetermined ratio. That is, it is most desirable to constitute first, so that granulation pharmaceutical preparation may be manufactured by mixing three kinds of granulation, after corning independently hydrophilic organic solvent extract granulation, water extract granulation, and supercritical extraction object granulation, respectively.
[0035] After carrying out disintegration of the hydrophilic organic solvent extract granulation by adding excipients, such as a lactose and a dextrin, to a hydrophilic organic solvent extract, it is corned by granularity according to a conventional method with granulator. Or it is also possible to corn by making the hydrophilic organic solvent extract by which sprayed the liquefied hydrophilic organic solvent extract on the front face of the raw material granulation beforehand corned by granularity by purified sucrose, corn starch, etc. directly using coating granulator, or disintegration was carried out adhere through a sizing agent, and making it dry after that. As for the content of the hydrophilic organic solvent extract contained in this granulation, it is desirable that it is 5 - 50 % of the weight in solid content. When the content of this hydrophilic organic solvent extract is less than 5 % of the weight, the active principle of amount sufficient in propolis constituent granulation pharmaceutical preparation cannot be made to contain. Conversely, in exceeding 50 % of the weight, disintegration and a granulation process become remarkably difficult.
[0036] Although water extract granulation can be considered as granulation by the same manufacture approach as the above-mentioned hydrophilic organic solvent extract granulation, after carrying out disintegration by the freeze-dry method, it can also be made into granularity using granulator. As for the content of the water extract contained in this water extract granulation, it is [at the same reason as the case of the above-mentioned hydrophilic organic solvent extract granulation] desirable that it is 5 - 50 % of the weight in solid content.
[0037] Supercritical extraction object granulation can be considered as granulation by the same manufacture approach as said hydrophilic organic solvent extract granulation. Furthermore, in case this supercritical extraction object granulation is manufactured, it is desirable to carry out disintegration of the supercritical extraction object of the shape of the shape of a paste and emulsified liquid beforehand. It is desirable to constitute so that disintegration of the antibonding agents, such as calcium and a silicon dioxide, may be added and carried out to this disintegration with said excipient. At this time, the content of the supercritical extraction object in supercritical extraction object powder is 15 - 25 % of the weight more preferably ten to 35% of the weight. When the content of this supercritical extraction object is less than 10 % of the weight, the active principle of amount sufficient in propolis constituent granulation pharmaceutical preparation cannot be made to contain. Conversely, in exceeding 35 % of the weight, disintegration and a granulation process become remarkably difficult.
[0038] furthermore, the blending ratio of coal of an antibonding agent — the supercritical extraction object 1 — receiving — a weight ratio — desirable — 0.01-2 — it is 0.05-1 more preferably. When the weight ratio of this antibonding agent is less than 0.01, in case disintegration of the supercritical extraction object is carried out, an oil content dissociates, or caking of powder arises. Conversely, when exceeding 2, the taste and a smell peculiar to propolis become weaker, and the quality of goods is spoiled. It is possible by preparing the granulation for these three kinds of every extraction methods according to an individual, mixing them, and considering as the propolis constituent of this operation gestalt to prevent effectively separation of the oil content that in a supercritical extraction object contained and generating of caking by adhesion of powder. [many]
[0039] Moreover, the content of the supercritical extraction object contained in this supercritical extraction object granulation is 5 - 20 % of the weight more preferably three to 35% of the weight. When the content of this supercritical extraction object is less than 3 % of the weight, the active principle of amount sufficient in propolis constituent granulation pharmaceutical preparation cannot be made to contain. Conversely, in exceeding 35 % of the weight, disintegration and a granulation process become remarkably difficult.
[0040] Furthermore, in the hydrophilic organic solvent extract granulation, water extract granulation, and supercritical extraction object granulation which corned respectively as mentioned above, considering as coating granulation is desirable by coating the front face of the granulation after granulation with a coating agent. In addition, as said coating agent, a dextrin or corn starch is used suitably. In being able to prevent easily the debasement by adhesion of the granulation pharmaceutical preparation at the time of preservation, or granulation at this time, it becomes possible to control suitably the distributed stage and absorption stage to the inside of the body of an active principle. It becomes possible in the case of the propolis constituent granulation pharmaceutical preparation which consists of three kinds of extract granulation especially, to arrange the peak of the bioactive manifestation in the inside of the body of three kinds of extracts, and to heighten the synergistic effect notably, since the

absorption stage to the inside of the body of an active principle is controllable for every granulation.
[0041] The coating granulation of a hydrophilic organic solvent extract makes the coating agent by which sprayed the liquefied coating agent on the front face of hydrophilic organic solvent extract granulation directly, or disintegration was carried out adhere through a sizing agent using coating granulator, and is prepared by making it dry after that. The propolis constituent granulation pharmaceutical preparation which corned after mixing three kinds of extracts before the coating granulation of a water extract, the coating granulation of a supercritical extraction object, and granulation is prepared similarly.
[0042] As for the ratio (comparatively) of the coating agent weight to the coating ratio of the coating granulation of a hydrophilic organic solvent extract, i.e., the solid content weight of coating granulation, it is desirable that it is 0.2-0.4. When this coating ratio is less than 0.2, since the decay time within the stomach is short, the time amount exposed to stomach juice becomes long, and it becomes easy to condense the component in a hydrophilic organic solvent extract. Consequently, it is hard coming to win popularity the emulsification operation by bile acid, and the absorption coefficient to the inside of the body falls. Conversely, in exceeding 0.4, since it does not fully collapse within the stomach, it is in the inclination which is in absorption of an active principle remarkably.
[0043] As for the coating ratio of the coating granulation of a water extract, it is desirable that it is 0.4-0.6. When this coating ratio is less than 0.4, the component in the water extract which exists near the front face of coating granulation absorbs moisture, and there is a possibility that adhesion of coating granulation may take place. Moreover, in the stomach, low-molecular matter, such as an organic acid, is eluted easily, and is diluted, and when the membrane permeability of an intestinal tract falls, there is also a possibility that the absorption coefficient to the inside of the body may fall. Conversely, when exceeding 0.6, sufficient anti-inflammation effectiveness is not demonstrated from the content of an active principle falling.
[0044] the coating ratio of the coating granulation of a supercritical extraction object -- desirable -- 0.05 to 0.2 -- it is 0.05-0.1 more preferably. When this coating ratio is less than 0.05, since the decay time within the stomach is short, the time amount exposed to stomach juice becomes long, and it becomes easy to condense the component in a supercritical extraction object. Conversely, in exceeding 0.2, it is in the inclination which is in absorption of an active principle remarkably, without fully collapsing within the stomach.
[0045] The effectiveness demonstrated according to the above-mentioned operation gestalt is indicated below.
- The propolis constituent of an operation gestalt contains three kinds of extracts of a hydrophilic organic solvent extract, a water extract, and a supercritical extraction object. Said each extract contains a mutually different active principle from being extracted with an extracting solvent (the extract approach) different, respectively. this propolis constituent -- ******** -- according to the synergistic effect of an active principle, as compared with the mixture of one kind of extract, or two kinds of extracts, the higher efficacy and the effectiveness as health food and cosmetics pharmaceutical preparation can be demonstrated, and the outstanding health food and cosmetics pharmaceutical preparation can be obtained.
[0046] Furthermore, this propolis constituent is the physiological active substance of the varieties which have the health promotion activity included in a propolis original lump since the matter which has the matter, the water-soluble oleophilic matter, and its water-soluble middle property contains, and the matter which can be extracted can be referred to as that all are included on parenchyma. For this reason, it not only can take in almost all the physiological active substances in propolis the same with taking in a propolis original lump the whole ****, but the constituent of the combination ratio of three kinds of said extracts can demonstrate efficacy still higher than the propolis original lump itself as the synergistic effect.
[0047] On the other hand, in JP,2001-78686,A, the attempt of propolis constituent preparation which added supercritical extraction propolis to alcoholic extract propolis and water extract propolis is also performed. However, for this attempt, it aims only at preparing the constituent which consists of three sorts of uniform extracts, and consideration is not paid at all about bringing the multiplication improvement effectiveness to the efficacy of an active principle. Furthermore, for the physiological active substance (active principle), the spray dryer which the temperature of goods of a constituent elevated-temperature-izes is used for the disintegration of the constituent containing the water extract propolis which very severe manufacture conditions are adopted, for example, is weakened at heat. For this reason, possibility the synergistic effect by three sorts of extracts is not not only expectable, but that efficacy will be reduced on the contrary is high.
[0048] - By having been extracted from the residue after a hydrophilic organic solvent extracts a propolis original lump as a water extract or a supercritical extraction object, the hydrophobic component which has the hydrophilic component or the extreme hydrophobicity which has an extreme hydrophilic property among the components extracted with a hydrophilic organic solvent overlaps into a propolis constituent, and does not contain so much. Since it was solved that there is work which controls the health promotion effectiveness etc. on the contrary when [which was depended on this invention persons] these components were wholeheartedly taken in so much at once as a result of research, as for the propolis constituent containing said water extract or a supercritical extraction object, the health promotion effectiveness can be demonstrated very good. In addition, the component located in the boundary region which may be extracted with supercritical extraction and water hardly exists. Since a propolis original lump's (propolis raw material) permeability is furthermore easily raised in an operation of a hydrophilic organic solvent at this time, in being able to perform easily the process which obtains that extract, it is possible to cut down raw material expense easily.
[0049] - The synergistic effect by three kinds of extracts can be demonstrated very effectively to the supercritical extraction object 1 weight section by carrying out 0.5-6 weight section content of 1 - 20 weight section and the water extract for a hydrophilic organic solvent extract. Furthermore, the synergistic effect by three kinds of extracts can be demonstrated much more notably by exceeding 10 weight sections for hydrophilic organic solvent extract propolis, and carrying out 1-5 weight section content of the water extract propolis below 18 weight sections to the supercritical extraction propolis 1 weight section.
[0050] - The propolis constituent of this operation gestalt is constituted so that hydrophilic organic solvent extract powder, water extract powder, and supercritical extraction object powder may be contained. That is, since each extract powder extracted by three kinds of different extraction methods is alike, respectively and disintegration is carried out on the most extremely stable conditions, this propolis constituent may exist as a constituent which did not cause deterioration of each extract powder and was unified more. Furthermore, this propolis constituent can hold very high quality from a powder property being remarkably high for a long period of time. Furthermore, the outstanding salability can be given to a product from it being easy to change freely the mixing ratio which can expect the outstanding synergistic effect at this time.
[0051] - The propolis constituent granulation pharmaceutical preparation of an operation gestalt contains the above-mentioned propolis constituent, and contains hydrophilic organic solvent extract granulation, water extract granulation, and supercritical extraction object granulation. For this reason, since it has the same presentation as the above-mentioned propolis constituent, the synergistic effect by three kinds of extracts can be demonstrated very effectively. Furthermore, degradation of the physical

properties by mixing of a different component is avoidable from it being granulation made to correspond to the physical properties of the extract for every extract, and in being able to prevent joining when a propolis constituent absorbs moisture effectively, the oil-soluble component in each extract can also prevent effectively the problem of dissociating at the time of mixing or preservation. Therefore, the propolis constituent granulation pharmaceutical preparation of very high quality can be offered by combining three kinds of extracts as granulation, respectively.

[0052] - When using a supercritical extraction object as granulation, it can manufacture easily by blending an antibonding agent 0.01-2 times by the weight ratio to the supercritical extraction object 1 beforehand. In the process which carries out disintegration of the supercritical extraction object of the shape of the shape of a paste, and emulsified liquid, separation of the oil content in a supercritical extraction object and generating of caking by adhesion of powder can be effectively prevented by using calcium as an antibonding agent especially.

[0053] In addition, it is possible by using the granulation of three kinds of said extracts as coating granulation, respectively to control the distributed stage and absorption stage to the inside of the body of each extract to arbitration. For this reason, while being able to promote further the absorption to the inside of the body of three kinds of extracts, the synergistic effect of the anti-inflammatory activity by three kinds of extracts can be heightened notably. The absorption and the synergistic effect to the inside of the body of each of said extract can be heightened remarkably notably by constituting the coating ratio of the coating granulation of a hydrophilic organic solvent extract, a water extract, and a supercritical extraction object especially, so that it may be set to 0.2 to 0.4, 0.4-0.6, and 0.05-0.2, respectively.

[0054] That is, in the absorption side of each extract, since a hydrophilic organic solvent extract is hydrophobicity, and distribution and the dissolution with the stomach are hard to be carried out, absorption within intestines tends to become slow. The water extract was in the condition of having diluted substantially with digestive juices when it shifted in an intestinal tract since it dissolved and distributed very promptly with the stomach, and since absorption within an intestinal tract was given to the concentration dependence target, the absorption coefficient suited the low inclination. Thus, when the absorption stage of three kinds of extracts did not gather, possibility that the additive effectiveness of each extract independent or two kinds of extracts will stop at being demonstrated, without the ability demonstrating sufficient synergistic effect was high. However, in the propolis constituent granulation pharmaceutical preparation containing the coating granulation of three kinds of extracts by which coating was carried out by said coating ratio, since the absorption stage to the inside of the body is appropriately controllable, the absorption stage of each extract is arranged and it becomes possible to carry out that it is easy to demonstrate those synergistic effects.

[0055]

[Example] Hereafter, the example and the example of a comparison which materialized said operation gestalt are explained.

(Example 1 of a comparison) After the grinder (Ishizaki Electrical machinery Factory ********) ground 6kg of propolis original lumps from Brazil, 30l. of 95 capacity % ethanol was added, and the stirring extract was carried out at the room temperature for 24 hours. Next, 27kg (8.9 % of the weight of solid content) of ethanol extracts of propolis was obtained by filtering the extract containing said propolis grinding object through a filter paper (No.2 [ADVANTEC Oriental]), and removing residue. Vacuum concentration of the obtained extract was carried out until it became 20% of the weight in the evaporator, and 12kg of ethanol extracts was obtained. Furthermore, concentration hardening by drying of the 3kg of this ethanol extract was carried out by reduced pressure, and 600g of ethanol extracts was obtained. It considered as ethanol extract powder by grinding this ethanol extract with a mortar.

[0056] (Example 2 of a comparison) 2kg of propolis residue after the ethanol extract obtained in the example 1 of a comparison was measured by solid content conversion, 20l. of water was added, and the stirring extract was carried out at 45 degrees C for 5 hours. Next, the extract containing said propolis residue was rough-filtered until the moisture of residue was lost with the cloth for rough filtration (polyester gray yarn textiles), and 19.0kg of rough filtrate was obtained. After adding and stirring 340g (silica 100F made from Central Silica) of diatomaceous earth to this rough filtrate, 18.7kg of filtrate was obtained by filtering again using a filter paper (No.2 [ADVANTEC Oriental]). Vacuum concentration of this filtrate was carried out until it became 20% of the weight in the evaporator, and 1.1kg of water extracts was obtained. 0.6kg of this water extract was freeze-dried using the freezing vacuum dryer. 120g of water extract powder was obtained by grinding the obtained freeze-drying object.

[0057] (Example 3 of a comparison) 1kg of propolis residue after the ethanol extract obtained in the example 1 of a comparison was measured by solid content conversion, and the supercritical fluid processor (Mitsubishi Kakoki Kaisha, Ltd. make) performed supercritical fluid processing for 2 hours. In addition, it extracted on conditions with the flow rate of 5kg/hour, an atmospheric pressure [maximum-pressure 345] (35.0MPa), and a temperature of 40 degrees C at this time, using a carbon dioxide as supercritical gas. 59.3g of supercritical extraction objects was obtained by mixing an extract to homogeneity.

[0058] (Example 4 of a comparison) After the grinder (********) ground 2kg of propolis original lumps from Brazil, 20l. of water was added and the stirring extract was carried out at 45 degrees C for 5 hours. Next, the extract containing said propolis grinding object was rough-filtered until the moisture of residue was lost with the cloth for rough filtration (polyester gray yarn textiles), and 17.0kg of rough filtrate was obtained. After adding and stirring 340g (silica 100F made from Central Silica) of diatomaceous earth to this rough filtrate, 16.5kg of filtrate was obtained by filtering again using a filter paper (No.2 [ADVANTEC Oriental]). Vacuum concentration of this filtrate was carried out until it became 20% of the weight in the evaporator, and 1.4kg of water extracts was obtained. 0.7kg of this water extract was freeze-dried using the freezing vacuum dryer. 140g of water extract powder was obtained by grinding the obtained freeze-drying object.

[0059] (Example 5 of a comparison) After the grinder (********) ground 1kg of propolis original lumps from Brazil, the supercritical fluid processor (Mitsubishi Kakoki Kaisha, Ltd. make) performed supercritical fluid processing for 2 hours. In addition, it extracted on conditions with the flow rate of 5kg/hour, an atmospheric pressure [maximum-pressure 345] (35.0MPa), and a temperature of 40 degrees C at this time, using a carbon dioxide as supercritical gas. 98.3g of supercritical extraction objects was obtained by mixing an extract to homogeneity.

[0060] (Example 1) 1.0g of supercritical extraction objects obtained in the example 3 of a comparison was mixed with 10.7g of ethanol extract powder obtained in the example 1 of a comparison, and 1.3g of water extract powder obtained in the example 2 of a comparison, and 13.0g of propolis constituents was obtained.

[0061] (Example 2) 1.0g of supercritical extraction objects obtained in the example 3 of a comparison was mixed with 12.0g of ethanol extract powder obtained in the example 1 of a comparison, and 4.5g of water extract powder obtained in the example 2 of a comparison, and 17.5g of propolis constituents was obtained.

[0062] (Example 3) 1.0g of supercritical extraction objects obtained in the example 3 of a comparison was mixed with 17.0g of ethanol extract powder obtained in the example 1 of a comparison, and 3.0g of water extract powder obtained in the example 2 of

a comparison, and 21.0g of propolis constituents was obtained.
[0063] (Example 4) 1.0g of supercritical extraction objects obtained in the example 3 of a comparison was mixed with 5.0g of ethanol extract powder obtained in the example 1 of a comparison, and 3.0g of water extract powder obtained in the example 2 of a comparison, and 9.0g of propolis constituents was obtained.
[0064] (Example 5) 1.0g of supercritical extraction objects obtained in the example 5 of a comparison was mixed with 10.7g of ethanol extract powder obtained in the example 1 of a comparison, and 1.3g of water extract powder obtained in the example 4 of a comparison, and 13.0g of propolis constituents was obtained.
[0065] (Example 6) 1.0g of supercritical extraction objects obtained in the example 5 of a comparison was mixed with 12.0g of ethanol extract powder obtained in the example 1 of a comparison, and 4.5g of water extract powder obtained in the example 4 of a comparison, and 17.5g of propolis constituents was obtained.
[0066] The radical prehension ability trial compared the active oxygen elimination operation which is a bioactive operation important as <radical prehension ability trial> health food pharmaceutical preparation and cosmetics pharmaceutical preparation.
[0067] The sample solution which dissolved respectively the class product of the examples 1-5 of a comparison and examples 1-6 by 0.001% of the weight of concentration into dehydrated ethanol was prepared. After adding 2ml of DPPH (1 and 1-diphenyl-2-picrylhydrazyl) dehydrated ethanol solutions of 60microM to 2ml of each sample solution, mixing to it and preparing the DPPH ethanol sample solution to it, it was made to react to it for 20 minutes at a room temperature. Then, the absorbance in the wavelength of 517nm of each DPPH ethanol sample solution was measured using the spectrophotometer (PERKIN ELMER UV Spectrometer Lambda40). Moreover, after performing this actuation, using water as contrast, the purple clearance capacity (rate of radical prehension (%)) of each DPPH ethanol sample solution was calculated by having made the absorbance at that time into 100%. In addition, it is shown that antioxidation activity is so high that the value of this rate of radical prehension is high. A result is shown in a table 1.
[0068]
[A table 1]

検体名	含有量（%）			ﾗｼﾞｶﾙ捕捉率（%）	阻害濃度 IC_{50}（重量%）	白血球貪食率（%）
	ｴﾀﾉｰﾙ抽出	水抽出	超臨界抽出			
比較例1	100	—	—	35.6	0.0030	120.2
比較例2	—	100	—	24.2	0.0029	125.5
比較例3	—	—	100	26.8	0.0033	120.0
比較例4	—	100	—	20.5	0.0030	—
比較例5	—	—	100	23.8	0.0035	—
実施例1	82.3	10.0	7.7	60.5	0.0010	163.9
実施例2	68.6	25.7	5.7	52.3	0.0012	154.2
実施例3	81.0	14.3	4.7	53.1	0.0011	155.3
実施例4	55.6	33.3	11.1	40.2	0.0015	135.8
実施例5	82.3	10.0	7.7	48.0	0.0015	—
実施例6	68.6	25.7	5.7	46.4	0.0015	—

Consequently, it was checked that the propolis constituent of the examples 1-6 containing three kinds of extracts has notably high antioxidation activity as compared with the constituent of the examples 1-5 of a comparison. Especially, it was checked that an active oxygen elimination operation of the propolis constituent of examples 1-3 is more high as compared with examples 4-6.
[0069] Carrying out the measurement comparison of the strength of the activity which checks the hyaluronidase operation which is one of the mechanisms of a <hyaluronidase inhibition activity trial> allergy manifestation compared the antiallergic operation.
[0070] The sample solution which dissolved respectively the class product of the examples 1-5 of a comparison and examples 1-6 in the 0.1M acetic-acid buffer solution (pH3.5) by 0.001 - 0.1% of the weight of various concentration was prepared. Next, hyaluronidase is poured distributively 0.125ml (1100 units (U)) every beforehand, and said each sample solution is added into the solution which kept it warm for 20 minutes at 37 degrees C, and it warmed for 20 minutes and was made to react at 37 more degrees C. Then, the acetic-acid buffer solution containing a hyaluronic acid potassium (1.5mg/(ml)) was added, and it was made to react for 40 minutes at 37 degrees C. It was made to color after a reaction halt, the absorbance in 585nm of each sample (sample) was measured, and it asked for the rate of hyaluronidase activity inhibition (%) by the formula with the one following. Moreover, this actuation was performed using the 0.1M acetic-acid buffer solution as contrast, and it considered as control.
[0071]
[Equation 1]

$$\text{阻害率} = \frac{(\text{コントロールの吸光度}) - (\text{サンプルの吸光度})}{(\text{コントロールの吸光度})} \times 100$$

Furthermore, it asked for the concentration IC 50 (% of the weight) which checks the hyaluronidase activity of control 50% using the value of the rate of hyaluronidase activity inhibition computed by the sample solution of said various concentration. A result is shown in the above-mentioned table 1. Consequently, it was checked that the propolis constituent of the examples 1-6 containing three kinds of extracts has the remarkable high inhibition effectiveness to hyaluronidase as compared with the constituent of the examples 1-5 of a comparison. Especially, it was checked that the propolis constituent of examples 1-3 has higher effectiveness as compared with examples 4-6.
[0072] In order to examine phagocytic activity of leukocyte as an index of a <phagocytic-activity-of-leukocyte trial> immunity activation operation, it examined about the phagocytic activity facilitatory effect of the rat leucocyte to the yeast fungus which became extinct. The sample solution which dissolved the constituent of the examples 1-3 of a comparison and examples 1-4 in dimethyl sulfoxide (DMSO) as a sample so that it might become 110microg [/ml] concentration, respectively was used. Moreover, the contrast sample solution was prepared similarly, using Krestin powder (product made from Sankyo Pharmaceuticals) as positive control.

[0073] First, glycogen was prescribed for the patient into the abdominal cavity of a Wistar system rat (before or after the weight of 220g). Blood removal **** of the rat was carried out 4 hours after, and after pouring in the physiological saline into **** and washing intraperitoneal, said penetrant removers were collected with the leucocyte which exists in intraperitoneal. After the phosphate buffer solution's (PBS's) having washed this penetrant remover twice and performing a cel count, cell suspension was prepared so that it might become 5x106 cell [/ml] concentration. Moreover, after making yeast extinction fungus liquid YEAST (Bakers yeast) TypeII (SIGMA company make) suspend in PBS beforehand so that it may become 0.2 capacity %, 0.1ml of rat blood serums was added, and the yeast extinction bacillus solution was prepared by carrying out autoclave sterilization processing for 15 minutes at 121 degrees C.
[0074] Next, 0.04ml of each sample solution was added to 0.2ml of said cell suspension, 0.1ml of said yeast extinction bacillus solutions was added to each reaction mixture which incubated for 10 minutes at the room temperature, and it incubated for 30 minutes at 37 degrees C. After cooling, it dissolved at 95 capacity % ethanol so that it might become about the basic fuchsin at 1% of the weight, and 0.05ml of Fuchsine stain solutions prepared by filtering with a 0.45-micrometer filter was added, and they were dyed. Moreover, this actuation was performed, using PBS as contrast. The number of cells (white blood cell count which carried out phagocytosis of the yeast fungus) finally dyed with the number of cells (white blood cell count which did not carry out phagocytosis of the yeast fungus) and Fuchsine stain solution which were not dyed with said Fuchsine stain solution was counted, and it asked for the rate of the number of cells which carried out phagocytosis of the yeast fungus to the rate of leucocyte phagocytosis (%), i.e., a total cell count. A result is shown in the above-mentioned table 1.
[0075] Consequently, as compared with the constituent of the examples 1-3 of a comparison, high leucocyte phagocytosis was demonstrated and, as for the propolis constituent of the examples 1-4 containing three kinds of extracts, the immunity activation operation was checked. It was checked that especially the phagocytic activity of leukocyte of the propolis constituent of examples 1-3 is very high. In addition, the rate of leucocyte phagocytosis of the Krestin powder as positive control was 150.4%.
[0076] (Example 7) It sprayed gradually, drying 250g of ethanol extracts of the example 1 of a comparison by the dried air using centrifugal floating mold coating granulator (Freund Industrial make) into 100g (non PARERU -101: trademark registration) of raw material granulation which consists of purified sucrose and corn starch under engine-speed 200r.p.m. and 80-degree C conditions. Corn-starch 210g was added gradually simultaneously, and 299g of ethanol extract granulation which made an ethanol extract and corn starch adhere to said raw material granulation front face was obtained.
[0077] Moreover, 67.5g of water extracts of the example 2 of a comparison was gradually sprayed on 100g of this raw material granulation on these conditions, drying at a dried air so that the temperature of goods may not exceed 50 degrees C. Corn-starch 12.5g was added gradually simultaneously, and 113.5g of water extract granulation which made a water extract and corn starch adhere to a raw material granulation front face was obtained. Moreover, under engine-speed 180r.p.m. and a room temperature, into 100g of raw material granulation, spraying 37.5g of 60% of the weight of corn-starch suspension, 75g [of supercritical extraction objects of the example 3 of a comparison] and corn-starch 57.5g beforehand used as content powder 17% of the weight was added gradually, it dried and 223.5g of supercritical extraction object granulation was obtained.
[0078] In addition, disintegration of said supercritical extraction object was performed as follows. After having mixed 20g of egg shell calcium in 25g of supercritical extraction objects of the example 3 of a comparison, mixing pineapple flow 55g further and considering as powder, 50g corn starch was mixed and 150g of content supercritical extraction object powder was produced 17% of the weight. Finally, 77.0g (10.7g as an ethanol extract) of said ethanol extract granulation, and 12.1g (1.3g as a water extract) of water extract granulation and 20g (1g as a supercritical extraction object) of supercritical extraction object granulation were mixed, and it considered as propolis constituent granulation pharmaceutical preparation.
[0079] (Example 8) Into 75g of ethanol extract granulation of an example 7, corn-starch 32.15g was added as a coating agent (coating), and 107.15g of coating granulation of an ethanol extract was obtained into it. In addition, the coating ratio of this granulation is 0.3. Moreover, corn-starch 50g was added as a coating agent into 50g of water extract granulation of an example 7, and 100g (a coating ratio is 0.5) of coating granulation of a water extract was obtained into it. Moreover, corn-starch 11.2g was added as a coating agent into 100g of supercritical extraction object granulation of an example 7, and 111.2g (a coating ratio is 0.10) of coating granulation of a supercritical extraction object was obtained into it. Finally, 110.2g (10.7g as an ethanol extract) of coating granulation of said ethanol extract, 24.1g (1.3g as a water extract) of coating granulation of a water extract, and 22.2g (1g as a supercritical extraction object) of coating granulation of a supercritical extraction object were mixed, and it considered as propolis constituent granulation pharmaceutical preparation.
[0080] In order to consider the edema depressant action used as the index of <edema inhibition test> anti-inflammatory activity, the acute inflammation model rat was produced, and it examined about the inflammation depressor effect. First, the day fast of the Wistar system rat (before or after the weight of 220g) was carried out, subcutaneous injection of the 0.1ml of the carrageenin solutions was carried out to the right rear crotch planta 1% of the weight, and the volume of a guide peg was measured 4 hours after. As a sample, the class product of the examples 1-3 of a comparison, examples 1-4, an example 7, and an example 8 was dissolved into 10% gum arabic solution, and it adjusted so that propolis (extract) concentration might become [ml] in 20mg /. 1 hour before carrageenin administration of each sample solution, 5 hours ago, the 3-hour front stirrup was administered orally so that it might be set to 200 mg/kg / 10ml, respectively. Moreover, sterilized water was used as contrast. And it asked for the rate of carrageenin edema control (%) from the measurement result of the volume of the guide peg of a rat. A result is shown in a table 2.
[0081]
[A table 2]

検体名	カラゲニン浮腫抑制率（%）			
	1時間前投与	3時間前投与	5時間前投与	平均
比較例1	3．4	38．2	30．2	23．9
比較例2	25．0	10．2	9．0	14．7
比較例3	5．3	44．2	15．6	21．7
実施例1	4．3	69．0	40．2	37．8
実施例2	13．2	55．7	33．6	34．1
実施例3	8．5	63．4	38．3	36．7
実施例4	15．6	40．5	29．1	28．4
実施例7	4．7	67．4	40．2	37．4
実施例8	3．4	66．3	50．8	40．2

Consequently, in the group which prescribed the propolis constituent granulation pharmaceutical preparation of the examples 1-4 containing three kinds of extracts, an example 7, and an example 8 for the patient 3 hours before carrageenin administration as compared with the constituent of the examples 1-3 of a comparison, remarkable high depressor effect was checked to the edema by acute inflammation. Although each extract (constituent of the examples 1-3 of a comparison) demonstrated anti-inflammatory activity (edema depressant action), respectively, it was checked that the propolis constituent (examples 1-4, an example 7, and example 8) which mixed three kinds of extracts demonstrates the anti-inflammation effectiveness heightened in multiplication. furthermore, the mixing ratio of an ethanol extract — while increasing the content of flavonoids by raising a rate, when the organic acids and polysaccharide which are contained in a water extract auxiliary, and the hydrophobic high matter (fats-and-oils component etc.) contained in a supercritical extraction object are added, anti-inflammatory activity can be raised much more notably.

[0082] On the other hand, depressor effect with the propolis constituent granulation pharmaceutical preparation of an example 8 more expensive than the granulation pharmaceutical preparation of an example 7 was checked. It is guessed that this phenomenon is what is depended on the contact to the gastric acid of the active principle contained in them having been controlled, and condensation having been prevented, having come to distribute within intestines, and the absorbed amount having increased from coating of ethanol extract granulation and the supercritical extraction object granulation being carried out remarkably. Furthermore, by making the coating ratio of water extract granulation increase, and delaying a distributed stage, the active principle comes to be mostly absorbed with the absorption stage of an ethanol extract and a supercritical extraction object at a coincidence term, and while the absorption stage of the active principle in three kinds of extracts gathers, what is depended on the absorbed amount having increased is conjectured. Therefore, the synergistic effect by the active principle in three kinds of extracts is expected to be because for it to have been demonstrated very notably.

[0083] In addition, it changes as follows and each above-mentioned operation gestalt can also take shape.

- Constitute to carry out the water extract of the residue, and to carry out supercritical extraction of the residue further after performing a hydrophilic organic solvent extract previously using a propolis original lump. Or constitute to carry out supercritical extraction of the residue, and to carry out the water extract of the residue further after performing a hydrophilic organic solvent extract previously using a propolis original lump. Thus, when constituted, the raw material expense reduction effectiveness can be demonstrated still more effectively.

[0084] Furthermore, the technical thought which can be grasped from said operation gestalt is indicated below.

- Propolis constituent given in either of claim 1 to claims 4 characterized by setting the blending ratio of coal of said hydrophilic organic solvent extract propolis, water extract propolis, and supercritical extraction propolis to 2-15:0.6-5:1 by the weight ratio.

[0085] - Propolis constituent granulation pharmaceutical preparation according to claim 5 characterized by using the granulation of said supercritical extraction propolis as the coating granulation of the coating ratios 0.05-0.2 while using the granulation of said hydrophilic organic solvent extract propolis as the coating granulation of the coating ratios 0.2-0.4 and using the granulation of said water extract propolis as the coating granulation of the coating ratios 0.4-0.6. However, said coating ratio shows the rate of coating agent weight to coating granulation weight.

[0086] - The granulation of said supercritical extraction propolis is propolis constituent granulation pharmaceutical preparation according to claim 5 characterized by blending and carrying out disintegration 0.01-2 at a weight ratio about an antibonding agent to the supercritical extraction propolis 1.

[0087] - Health food pharmaceutical preparation characterized by containing the propolis constituent of a publication in either of claim 1 to claims 4. Thus, when constituted, the health food pharmaceutical preparation which can demonstrate efficacy high as health food and cosmetics can be offered cheaply efficiently.

[0088] - Cosmetics pharmaceutical preparation characterized by containing the propolis constituent of a publication in either of claim 1 to claims 4. Thus, when constituted, the cosmetics pharmaceutical preparation which can demonstrate efficacy high as health food and cosmetics can be offered cheaply efficiently.

[0089] - Health food pharmaceutical preparation characterized by containing propolis constituent granulation according to claim 5. Thus, when constituted, while being able to demonstrate efficacy high as health food and cosmetics, the health food excellent in stability can be offered.

[0090] - At least one sort which is a propolis constituent containing hydrophilic organic solvent extract propolis, water extract propolis, and supercritical extraction propolis, and is chosen from said water extract propolis and supercritical extraction propolis is a propolis constituent characterized by being extracted from the residue after a hydrophilic organic solvent extracts a propolis original lump. Thus, when constituted, efficacy high as health food and a cosmetics raw material can be demonstrated.

[0091]

[Effect of the Invention] According to this invention, the following effectiveness is done so as explained in full detail above. According to propolis constituent granulation pharmaceutical preparation according to claim 5, efficacy high as health food and a cosmetics raw material can be demonstrated in the propolis constituent of invention according to claim 4, and a list from claim 1.

[Translation done.]

* NOTICES *

1.This document has been translated by computer. So the translation may not reflect the original precisely.
2.**** shows the word which can not be translated.
3.In the drawings, any words are not translated.

TECHNICAL FIELD

[Field of the Invention] This invention relates to the propolis constituent used as health food pharmaceutical preparation, cosmetics pharmaceutical preparation, etc., and the propolis constituent granulation pharmaceutical preparation containing that constituent.

[Translation done.]

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PRIOR ART

[Description of the Prior Art] propolis (propolis original lump) -- a bee -- it is the matter of the shape of the shape of resin which is also called tar and constitutes **** of the blow hole of an Apis mellifrera, and wax. A honeybee is sap and the plant body which have been extracted from surrounding vegetation, beeswax and pollen are often mixed, and generally this propolis presents blackish brown thru/or dark brown, and contains various components.
[0003] Although this propolis had been used as a raw material of drugs or health food in Europe for many years, it came to be used for many products as a raw material of health food or cosmetics also in Japan in recent years. As main bioactive of propolis, active oxygen elimination ability and an immunity activation operation are known, and the efficacy as a raw material of health food is supported. Moreover, quenching, the analgesic action, the antiallergic operation, and the antibacterial action to the disease germ of the large range are also known. It is reported at an institute especially that there are remarkable anticancer and antitumor action, and since the discovery report of two or more new cancericidal material was carried out out of the component, the efficacy which was excellent in propolis will attract attention of a world suddenly.
[0004] TERUPE ** with a still lower polarity, such as flavonoids from an organic-acid compound with a polarity high as a chemical entity contained in this propolis, and polyphenol, -- the id -- very many compounds, such as a kind, are checked. It is thought that the bioactive which the bioactive of these matter acts intricately, has it and was excellent in propolis is formed.
[0005] Since the propolis original lump is very difficult, it is [taking in in the condition as it is] common to be taken in as an extract extracted with a hydrophilic organic solvent or water, such as ethanol. Various physiological active substances contain in the hydrophilic organic solvent extract or water extract of this propolis, and various products which used that pharmacological action in the health food field are marketed. Moreover, in JP,2000-325032,A, it is indicated by alcoholic extract propolis by adding and mixing water extract propolis gradually about the propolis product which carried out precipitation filtration and removed the resinous principle peculiar to alcoholic extract propolis. And this propolis product supposes that it is suitable for drink as compared with the propolis extract extracted with the independent solvent (alcohol or water) in the synergistic effect of each component being expectable while conquering the difficulty which each of alcoholic extract propolis and water extract propolis has.

[Translation done.]

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EFFECT OF THE INVENTION

[Effect of the Invention] According to this invention, the following effectiveness is done so as explained in full detail above. According to propolis constituent granulation pharmaceutical preparation according to claim 5, efficacy high as health food and a cosmetics raw material can be demonstrated in the propolis constituent of invention according to claim 4, and a list from claim 1.

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TECHNICAL PROBLEM

[Problem(s) to be Solved by the Invention] However, with the propolis product containing said alcoholic conventional extract propolis and water extract propolis, only the component meltable to alcohol among the components in a propolis original lump and the component meltable in water were contained, but many active principles are lost by moreover removing a resinous principle in a precipitation filtration process, and a part of propolis active principle was able to be taken in. For this reason, compared with the bioactive synergistic effect by many active principles when taking in a propolis original lump the whole ****, it was remarkable and said synergistic effect was low.
[0007] This invention is made paying attention to the trouble which exists in the above conventional techniques. The place made into the object is to offer the propolis constituent constituted so that efficacy high as health food and a cosmetics raw material could be demonstrated, and its granulation pharmaceutical preparation.

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MEANS

[Means for Solving the Problem] In order to attain the above-mentioned object, the propolis constituent of invention according to claim 1 is a propolis constituent containing hydrophilic organic solvent extract propolis, water extract propolis, and supercritical extraction propolis, and is characterized by carrying out 0.5-6 weight section content of 1 - 20 weight section and the water extract propolis for hydrophilic organic solvent extract propolis to the supercritical extraction propolis 1 weight section.
[0009] At least one sort as which the propolis constituent of invention according to claim 2 is chosen from said water extract propolis and supercritical extraction propolis in invention according to claim 1 is characterized by being extracted from the residue after a hydrophilic organic solvent extracts a propolis original lump.
[0010] The propolis constituent of invention according to claim 3 is characterized by exceeding 10 weight sections for hydrophilic organic solvent extract propolis, and carrying out 1-5 weight section content of the water extract propolis below 18 weight sections to the supercritical extraction propolis 1 weight section, in invention according to claim 1 or 2.
[0011] The propolis constituent of invention according to claim 4 is characterized by containing the hydrophilic organic solvent extract powder which carried out disintegration of said hydrophilic organic solvent extract propolis to either of claim 1 to claims 3 in invention of a publication, the water extract powder which carried out disintegration of said water extract propolis, and the supercritical extraction object powder which carried out disintegration of said supercritical extraction propolis.
[0012] The propolis constituent granulation pharmaceutical preparation of invention according to claim 5 The hydrophilic organic solvent extract granulation which is the propolis constituent granulation pharmaceutical preparation which contains the propolis constituent of a publication in either of claim 1 to claims 4, and corned said hydrophilic organic solvent extract propolis to granularity, It is characterized by containing the water extract granulation which corned said water extract propolis to granularity, and the supercritical extraction object granulation which corned said supercritical extraction propolis to granularity.
[0013]
[Embodiment of the Invention] Hereafter, the operation gestalt which materialized this invention is explained to a detail. The propolis constituent of an operation gestalt contains hydrophilic organic solvent extract propolis (it is hereafter indicated as a hydrophilic organic solvent extract), water extract propolis (it is hereafter indicated as a water extract), and supercritical extraction propolis (it is hereafter indicated as a supercritical extraction object). the gestalt of pharmaceutical preparation of versatility [constituent / this / propolis], such as health food pharmaceutical preparation and cosmetics pharmaceutical preparation, — taking orally — or dermal administration is carried out and it is used. A very high health promotion operation and the cosmetics effectiveness are demonstrated according to the synergistic effect of the active principle contained in three kinds of extracts by the extract approach that these propolis constituents differ. Said health promotion operation and the cosmetics effectiveness are presumed and checked by carrying out the measurement comparison of the radical prehension acceleration activity used as the index of edema control activity, hyaluronidase inhibition activity, leucocyte phagocytosis acceleration activity, and active oxygen elimination ability.
[0014] Three kinds of respectively separate propolis original lumps are prepared, and the start raw material (it is hereafter indicated as a propolis raw material) for extracting each extract can be used for three kinds of extract operation. However, when the workability of an extract process and the recovery (profitability) of an active principle are taken into consideration, it is desirable to constitute so that two or more kinds of extract operation may extract a propolis original lump. That is, after a hydrophilic organic solvent extracts a propolis original lump first, a water extract or supercritical extraction may be presented with the residue (residue of insolubility [organic solvent / hydrophilic]), and a hydrophilic organic solvent extract or a water extract may be presented with the residue after carrying out supercritical extraction to reverse.
[0015] the residue (residue) after performing a hydrophilic organic solvent extract previously most preferably using a propolis original lump — a water extract — or it is good to constitute so that supercritical extraction may be carried out. Since the hydrophobic component located in the boundary region which may be extracted with the hydrophilic component located in the boundary region which may be extracted with water and a hydrophilic organic solvent at this time or supercritical extraction, and a hydrophilic organic solvent overlaps into a propolis constituent and does not contain, it is easy to reduce the depressor effect over the health promotion effectiveness etc. That is, when said hydrophilic component or a hydrophobic component is taken in so much at once, there is work which controls health promotion on the contrary. Moreover, since permeability is good in the operation of a hydrophilic organic solvent, the residue after presenting a hydrophilic organic solvent extract previously can raise easily the yield in a subsequent water extract or supercritical extraction.
[0016] In addition, although anything of places of production, such as Brazil, China, Japan, the U.S., and Europe, of said propolis original lump is usable, it is desirable especially to use the product from Brazil with high extract yield in a water extract.
[0017] Although a hydrophilic organic solvent extract is obtained by extracting a meltable component to the hydrophilic organic solvent in a propolis raw material, using a hydrophilic organic solvent or its water diluent as an extracting solvent, it is desirable to use ethanol for manufacture of the constituent as health food as a hydrophilic organic solvent. Various active principles, such as flavonoids, polyphenol, organic acids, and Tell ** NOIDO, are contained in this hydrophilic organic solvent extract, and a health promotion operation of an active oxygen elimination operation, an immunity activation operation, quenching, an anticancer operation, etc. is demonstrated.
[0018] Considering that they carry out taking orally, using the property and propolis constituent of a solvent as food, said hydrophilic organic solvent has the most desirable ethanol, although they can use it, ketones which have the property dissolved in water, such as an acetone besides lower alcohol, such as ethanol, a methanol, and isopropanol, and a methyl ethyl ketone, choosing it suitably, the time of using ethanol as a hydrophilic organic solvent -- the concentration — desirable — 60 to 100

capacity % — it is 80 to 100 capacity % more preferably. When this concentration is under 60 capacity %, it is a ratio suitable for the configuration of this operation gestalt, and an active principle meltable to ethanol cannot be extracted efficiently. the amount of the ethanol used -- a propolis raw material — receiving — desirable — the amount of one to 20 times — more — desirable -- the amount of two to 10 times — it is the amount of three to 8 times still more preferably. When this amount used is under the amount of 1 time, the yield of an active principle falls. Conversely, in exceeding an amount 20 times, equipment not only becomes large superfluously, but starting workability falls [time amount] to processes, such as concentration, remarkably.

[0019] The temperature 10-30 degrees C near ordinary temperature is sufficient as extract temperature, and it is good to perform extract operation for 24 hours or more, stirring at the extract temperature. In addition, when said extract temperature is less than 10 degrees C, the yield of an active principle falls. Conversely, in exceeding 30 degrees C, the filterability after an extract worsens and workability falls. And after fully extracting an active principle by the above-mentioned extraction condition, hydrophilic organic solvent extract liquid is obtained by performing filter paper filtration or diatomaceous earth filtration. A hydrophilic organic solvent extract is obtained by evaporating and drying the solvent of this hydrophilic organic solvent extract liquid. Since powder physical properties are inferior, after [brown] accepting the need and diluting and condensing said hydrophilic organic solvent extract liquid, it dries, and excipients, such as a lactose and a dextrin, are added and it is [this hydrophilic organic solvent extract carries out disintegration and] good [it is, it carries out and is a dark-brown resin-like solid-state, if this is ground, pure hydrophilic organic solvent extract powder will be obtained but] also as hydrophilic organic solvent extract powder.

[0020] A water extract is obtained by extracting a meltable component in the water in a propolis raw material, using water as an extracting solvent. Various active principles, such as organic acids, polysaccharide, and protein, are contained in this water extract, and a health promotion operation of an antioxidation operation, a radical prehension acceleration operation, hyaluronidase inhibition activity, an anticancer operation, etc. is demonstrated. the amount of the extracting solvent used — a propolis raw material — receiving — desirable — the amount of one to 20 times — more — desirable — the amount of two to 15 times — it is the amount of five to 12 times still more preferably. When the amount of this extracting solvent used is under the amount of 1 time, the yield of an active principle falls. Conversely, in exceeding an amount 20 times, starting workability falls [time amount] to processes, such as concentration, remarkably.

[0021] 20-90 degrees C of 30-80 degrees C of extract temperature are 40-60 degrees C still more preferably more preferably. When this extract temperature is less than 20 degrees C, it not only causes deterioration of quality, but an extract process takes a long time and the yield of an active principle falls. Conversely, when exceeding 90 degrees C, it is expected that the denaturation of an active principle takes place and the synergistic effect falls. Moreover, although extract time amount is based also on the amount of the extracting solvent used, in order to extract sufficient quantity of an active principle, it is desirable to apply for 2 hours or more and to extract.

[0022] And after fully extracting an active principle by the above-mentioned extraction condition, water extract liquid is obtained by performing filter paper filtration or diatomaceous earth filtration. Furthermore, if it freeze-dries if needed after condensing this water extract liquid, pure water extract freeze-drying powder will be obtained. In order to obtain powder with still more sufficient physical properties, it is good also as water extract freeze-drying powder which freeze-dried after adding excipients, such as a lactose and a dextrin, in the aforementioned water extract liquid, and was excellent in the powder property. Moreover, even if it adds excipients, such as a lactose and a dextrin, to the aforementioned pure water extract freeze-drying powder, water extract freeze-drying powder with a sufficient powder property (it is hereafter indicated as water extract powder) is obtained.

[0023] A supercritical extraction object extracts a predetermined component from a propolis raw material by contacting the supercritical fluid and the propolis raw material which changed supercritical fluid into the supercritical condition under the conditions more than critical temperature and more than the critical pressure using well-known supercritical-fluid-extraction equipment. When using a carbon dioxide as supercritical fluid, the carbon dioxide which changed into the supercritical fluid condition as more than the critical temperature of 31.1 degrees C and more than the critical pressure of 72.8 atmospheric pressures (7.4MPa) extracts a propolis raw material. Flavonoids, Tell ** NOIDO, other hydrophobic physiological active substances, etc. are contained in the supercritical extraction object using this carbon dioxide, and demonstrating a health promotion operation of hyaluronidase inhibition activity, an anticancer operation, edema depressant action, etc. is checked.

[0024] Although ethane, a propane, a carbon dioxide, nitrous oxide, etc. are usable, as for said supercritical fluid, it is most desirable to use a carbon dioxide. this carbon dioxide suits the compound for an extract that a polarity is lower than ethanol in a top with the critical temperature near ordinary temperature — it has physical and chemical property. Since the physical properties in an extract process are not only excellent in this way, but a carbon dioxide does not affect the taste of a supercritical extraction product by tasteless and no odor, as supercritical fluid used for this operation gestalt, its carbon dioxide is the most desirable.

[0025] In order that supercritical fluid may use a consistency and the property in which solubility changes a lot, to few temperature gradients and a pressure differential [near the critical point], the suitable vertical width of face for the temperature and the pressure of processing is required for actuation in supercritical fluid extraction. 32-80 degrees C of operating temperature in the case of using a carbon dioxide are 32-50 degrees C more preferably. Moreover, the actuation pressure is 73 to 400 atmospheric pressure (7.4-40.5MPa) more preferably 73 to 500 atmospheric pressure (7.4-50.7MPa). 1-10kg (the rate of flow) /of flow rates of the carbon dioxide as supercritical fluid is [hour] 3-7kg/hour more preferably to 1kg of propolis raw materials. Although the processing time changes with the amounts and conditions of a propolis raw material, it can be suitably determined from a test or a processing track record by checking the time amount which an extract completes.

[0026] And the description of the supercritical extraction object of the propolis extracted by the above-mentioned extraction condition changes also with the elapsed time of an extract. Although many are pastes-like, a part may be obtained as powder thru/or a massive solid-state. When using ethanol as an entrainer, it becomes liquefied including ethanol. The carbon dioxide which the ethanol by which it is contained in extraction feed immediately after an extract, the ethanol as an entrainer, etc. were contained, and also the supercritical extraction object solidified by adiabatic expansion is contained. Since it is obtained as an uneven extract with the presentation which furthermore changes with extract elapsed time, after removing ethanol and a carbon dioxide and considering as a solid supercritical extraction object, stirring to homogeneity, if it grinds, it will become pure supercritical extraction object powder. In order to give a further more good powder property, it is good also as supercritical extraction object powder which added and carried out disintegration of the excipients, such as a lactose and a dextrin, to the supercritical extraction object if needed.

[0027] the blending ratio of coal of the hydrophilic organic solvent extract in the propolis constituent of this operation gestalt — the supercritical extraction object 1 weight section — receiving — desirable — 1 - 20 weight section — 10 weight sections are

exceeded more preferably and they are below 18 weight sections. To the supercritical extraction object 1 weight section, when the blending ratio of coal of a hydrophilic organic solvent extract is under 1 weight section, the sufficient efficacy and the effectiveness as health food or cosmetics pharmaceutical preparation cannot be demonstrated. Conversely, when the blending ratio of coal of a hydrophilic organic solvent extract exceeds 20 weight sections to the supercritical extraction object 1 weight section, since the content of the supercritical extraction object to a water extract falls relatively, the synergistic effect of these water extract and a supercritical extraction object is not fully demonstrated.

[0028] the blending ratio of coal of the water extract in the propolis constituent of this operation gestalt — the supercritical extraction object 1 weight section — receiving — desirable — 0.5 - 6 weight section — it is 1 - 5 weight section more preferably. To the supercritical extraction object 1 weight section, when the blending ratio of coal of a water extract is under the 0.5 weight section, the sufficient efficacy and the effectiveness as health food or cosmetics pharmaceutical preparation cannot be demonstrated. Conversely, when the blending ratio of coal of a water extract exceeds 6 weight sections to the supercritical extraction object 1 weight section, since the content of the supercritical extraction object to a hydrophilic organic solvent extract falls relatively, the synergistic effect of these hydrophilic-properties organic solvent extract and a supercritical extraction object is not fully demonstrated.

[0029] the propolis constituent constituted as mentioned above — as health food pharmaceutical preparation, cosmetics pharmaceutical preparation, etc. — taking orally — or dermal administration is carried out and it is used. In this propolis constituent, within limits which do not spoil the health promotion effectiveness of the above-mentioned active principle in that case For example, plumping agents, such as excipients, such as a dextrin, cyclodextrin, and a lactose, and a sodium hydrogencarbonate, Brighteners, such as a cull navarho, a shellac, and yellow bees wax, a pectin carboxymethyl cellulose, Gelling agents, such as agar and starch, an alginic acid, carrageenan, xanthan gum, Thickeners, such as chitosan, sugar, honey, a liquorice extract, a stevia, saccharin sodium, Sweetening agents, such as an oligosaccharide, erythritol, a starch syrup, and isomerized sugar, a quillaja extract, Emulsifiers, such as lecithin, a glycerol, a glycerine fatty acid ester, and an soybean saponin, pH regulators, such as coloring matter, such as flavorings, such as cinnamon essential oil, jasmine essential oil, rosemary essential oil, and lime essential oil, a caramel, a red cabbage, a gardenia, nonuniformity SAKIIMO, a grape, and curcmae rhizoma, a lactic acid, a lactate, a citric acid, a malic acid, and a sodium carbonate, may be added.

[0030] As health food pharmaceutical preparation, by adding the above-mentioned propolis constituent in a food raw material, a drink article raw material, or a drugs raw material, it is processed into configurations, such as the shape of the shape of powder, a liquid, granularity, a tablet, and a capsule, and a stick, and is used as health food, a health drink, or quasi drugs. It is used as quasi drugs, being blended with soap, gear-tooth polishing powder, etc. As cosmetics pharmaceutical preparation, by adding the above-mentioned propolis constituent for a food raw material, a drink article raw material, or a cosmetics raw material, it is processed into the shape of a liquid, a milk liquid, and a half-solid, and the configuration of powdered **, and is used as cosmetics food, a cosmetics drink, or cosmetics. According to the class of makeup, as for said cosmetics, alcohols, a fats-and-oils surfactant, purified water, etc. are added suitably.

[0031] On the other hand, it is processed into many gestalten, such as a tablet, a capsule, granulation, powder, syrups, and drinkable preparations, when using this propolis constituent as an oral agent. When processing it into a tablet and a capsule, a binder, an excipient, a plumping agent, a brightener, a sweetening agent, a flavor agent, etc. are added suitably. A tablet can also be covered with a shellac or sugar. Moreover, the above-mentioned ingredient can be made to contain liquid support, such as fats and oils, further in the case of a capsule. On the other hand, when using as a parenteral agent, it is used with the gestalt of external preparations, such as an ointment, cream pharmaceuticals, and liquor, carrying out dermal administration. As a basis of these external preparations, vaseline, paraffin, fats and oils, lanolin, macro gall, etc. are used suitably, and can consider as an ointment, cream pharmaceuticals, etc. by the usual approach.

[0032] It is desirable to consider as granularity granulation pharmaceutical preparation with big particle diameter on the other hand, since possibility that the component in a propolis constituent will join during preservation according to moisture absorption etc. is high when the above-mentioned propolis constituent is made into the shape of powder and powder of especially minute particle diameter.

[0033] in considering this propolis constituent as granulation pharmaceutical preparation, after mixing three kinds of extracts — disintegration — carrying out — granulator — a law — according to a method, it can fabricate to granularity, and can consider as granulation pharmaceutical preparation. Or mixing three kinds of extracts by which disintegration was carried out using granulator, it can corn to granularity and can also consider as granulation pharmaceutical preparation. Or it is also possible to consider as propolis constituent granulation pharmaceutical preparation by mixing spraying directly the liquid (liquefied propolis constituent) which mixed three kinds of extracts on the front face of the raw material granulation beforehand corned by granularity by purified sucrose, corn starch, etc., or making three kinds of extracts by which disintegration was carried out adhere to it through a sizing agent using coating granulator, and making it dry after that.

[0034] However, since possibility that problems, such as separation, will arise according to a difference of the properties (strength of lipophilicity etc.) of each extract by the manufacture approach of the above-mentioned granulation pharmaceutical preparation at the time of mixing or preservation is high, after making it granularity for every extract, considering as granulation pharmaceutical preparation is most desirable by mixing by the predetermined ratio. That is, it is most desirable to constitute first, so that granulation pharmaceutical preparation may be manufactured by mixing three kinds of granulation, after corning independently hydrophilic organic solvent extract granulation, water extract granulation, and supercritical extraction object granulation, respectively.

[0035] After carrying out disintegration of the hydrophilic organic solvent extract granulation by adding excipients, such as a lactose and a dextrin, to a hydrophilic organic solvent extract, it is corned by granularity according to a conventional method with granulator. Or it is also possible to corn by making the hydrophilic organic solvent extract by which sprayed the liquefied hydrophilic organic solvent extract on the front face of the raw material granulation beforehand corned by granularity by purified sucrose, corn starch, etc. directly using coating granulator, or disintegration was carried out adhere through a sizing agent, and making it dry after that. As for the content of the hydrophilic organic solvent extract contained in this granulation, it is desirable that it is 5 - 50 % of the weight in solid content. When the content of this hydrophilic organic solvent extract is less than 5 % of the weight, the active principle of amount sufficient in propolis constituent granulation pharmaceutical preparation cannot be made to contain. Conversely, in exceeding 50 % of the weight, disintegration and a granulation process become remarkably difficult.

[0036] Although water extract granulation can be considered as granulation by the same manufacture approach as the above-mentioned hydrophilic organic solvent extract granulation, after carrying out disintegration by the freeze-dry method, it can also

be made into granularity using granulator. As for the content of the water extract contained in this water extract granulation, it is [at the same reason as the case of the above-mentioned hydrophilic organic solvent extract granulation] desirable that it is 5 - 50 % of the weight in solid content.
[0037] Supercritical extraction object granulation can be considered as granulation by the same manufacture approach as said hydrophilic organic solvent extract granulation. Furthermore, in case this supercritical extraction object granulation is manufactured, it is desirable to carry out disintegration of the supercritical extraction object of the shape of the shape of a paste and emulsified liquid beforehand. It is desirable to constitute so that disintegration of the antibonding agents, such as calcium and a silicon dioxide, may be added and carried out to this disintegration with said excipient. At this time, the content of the supercritical extraction object in supercritical extraction object powder is 15 - 25 % of the weight more preferably ten to 35% of the weight. When the content of this supercritical extraction object is less than 10 % of the weight, the active principle of amount sufficient in propolis constituent granulation pharmaceutical preparation cannot be made to contain. Conversely, in exceeding 35 % of the weight, disintegration and a granulation process become remarkably difficult.
[0038] furthermore, the blending ratio of coal of an antibonding agent -- the supercritical extraction object 1 -- receiving -- a weight ratio -- desirable -- 0.01-2 -- it is 0.05-1 more preferably. When the weight ratio of this antibonding agent is less than 0.01, in case disintegration of the supercritical extraction object is carried out, an oil content dissociates, or caking of powder arises. Conversely, when exceeding 2, the taste and a smell peculiar to propolis become weaker, and the quality of goods is spoiled. It is possible by preparing the granulation for these three kinds of every extraction methods according to an individual, mixing them, and considering as the propolis constituent of this operation gestalt to prevent effectively separation of the oil content that in a supercritical extraction object contained and generating of caking by adhesion of powder. [many]
[0039] Moreover, the content of the supercritical extraction object contained in this supercritical extraction object granulation is 5 - 20 % of the weight more preferably three to 35% of the weight. When the content of this supercritical extraction object is less than 3 % of the weight, the active principle of amount sufficient in propolis constituent granulation pharmaceutical preparation cannot be made to contain. Conversely, in exceeding 35 % of the weight, disintegration and a granulation process become remarkably difficult.
[0040] Furthermore, in the hydrophilic organic solvent extract granulation, water extract granulation, and supercritical extraction object granulation which corned respectively as mentioned above, considering as coating granulation is desirable by coating the front face of the granulation after granulation with a coating agent. In addition, as said coating agent, a dextrin or corn starch is used suitably. In being able to prevent easily the debasement by adhesion of the granulation pharmaceutical preparation at the time of preservation, or granulation at this time, it becomes possible to control suitably the distributed stage and absorption stage to the inside of the body of an active principle. It becomes possible in the case of the propolis constituent granulation pharmaceutical preparation which consists of three kinds of extract granulation especially, to arrange the peak of the bioactive manifestation in the inside of the body of three kinds of extracts, and to heighten the synergistic effect notably, since the absorption stage to the inside of the body of an active principle is controllable for every granulation.
[0041] The coating granulation of a hydrophilic organic solvent extract makes the coating agent by which sprayed the liquefied coating agent on the front face of hydrophilic organic solvent extract granulation directly, or disintegration was carried out adhere through a sizing agent using coating granulator, and is prepared by making it dry after that. The propolis constituent granulation pharmaceutical preparation which corned after mixing three kinds of extracts before the coating granulation of a water extract, the coating granulation of a supercritical extraction object, and granulation is prepared similarly.
[0042] As for the ratio (comparatively) of the coating agent weight to the coating ratio of the coating granulation of a hydrophilic organic solvent extract, i.e., the solid content weight of coating granulation, it is desirable that it is 0.2-0.4. When this coating ratio is less than 0.2, since the decay time within the stomach is short, the time amount exposed to stomach juice becomes long, and it becomes easy to condense the component in a hydrophilic organic solvent extract. Consequently, it is hard coming to win popularity the emulsification operation by bile acid, and the absorption coefficient to the inside of the body falls. Conversely, in exceeding 0.4, since it does not fully collapse within the stomach, it is in the inclination which is in absorption of an active principle remarkably.
[0043] As for the coating ratio of the coating granulation of a water extract, it is desirable that it is 0.4-0.6. When this coating ratio is less than 0.4, the component in the water extract which exists near the front face of coating granulation absorbs moisture, and there is a possibility that adhesion of coating granulation may take place. Moreover, in the stomach, low-molecular matter, such as an organic acid, is eluted easily, and is diluted, and when the membrane permeability of an intestinal tract falls, there is also a possibility that the absorption coefficient to the inside of the body may fall. Conversely, when exceeding 0.6, sufficient anti-inflammation effectiveness is not demonstrated from the content of an active principle falling.
[0044] the coating ratio of the coating granulation of a supercritical extraction object -- desirable -- 0.05 to 0.2 -- it is 0.05-0.1 more preferably. When this coating ratio is less than 0.05, since the decay time within the stomach is short, the time amount exposed to stomach juice becomes long, and it becomes easy to condense the component in a supercritical extraction object. Conversely, in exceeding 0.2, it is in the inclination which is in absorption of an active principle remarkably, without fully collapsing within the stomach.
[0045] The effectiveness demonstrated according to the above-mentioned operation gestalt is indicated below.
- The propolis constituent of an operation gestalt contains three kinds of extracts of a hydrophilic organic solvent extract, a water extract, and a supercritical extraction object. Said each extract contains a mutually different active principle from being extracted with an extracting solvent (the extract approach) different, respectively. this propolis constituent -- ******** -- according to the synergistic effect of an active principle, as compared with the mixture of one kind of extract, or two kinds of extracts, the higher efficacy and the effectiveness as health food and cosmetics pharmaceutical preparation can be demonstrated, and the outstanding health food and cosmetics pharmaceutical preparation can be obtained.
[0046] Furthermore, this propolis constituent is the physiological active substance of the varieties which have the health promotion activity included in a propolis original lump since the matter which has the matter, the water-soluble oleophilic matter, and its water-soluble middle property contains, and the matter which can be extracted can be referred to as that all are included on parenchyma. For this reason, it not only can take in almost all the physiological active substances in propolis the same with taking in a propolis original lump the whole ****, but the constituent of the combination ratio of three kinds of said extracts can demonstrate efficacy still higher than the propolis original lump itself as the synergistic effect.
[0047] On the other hand, in JP,2001-78686,A, the attempt of propolis constituent preparation which added supercritical extraction propolis to alcoholic extract propolis and water extract propolis is also performed. However, for this attempt, it aims only at preparing the constituent which consists of three sorts of uniform extracts, and consideration is not paid at all about

bringing the multiplication improvement effectiveness to the efficacy of an active principle. Furthermore, for the physiological active substance (active principle), the spray dryer which the temperature of goods of a constituent elevated-temperature-izes is used for the disintegration of the constituent containing the water extract propolis which very severe manufacture conditions are adopted, for example, is weakened at heat. For this reason, possibility the synergistic effect by three sorts of extracts is not not only expectable, but that efficacy will be reduced on the contrary is high.

[0048] - By having been extracted from the residue after a hydrophilic organic solvent extracts a propolis original lump as a water extract or a supercritical extraction object, the hydrophobic component which has the hydrophilic component or the extreme hydrophobicity which has an extreme hydrophilic property among the components extracted with a hydrophilic organic solvent overlaps into a propolis constituent, and does not contain so much. Since it was solved that there is work which controls the health promotion effectiveness etc. on the contrary when [which was depended on this invention persons] these components were wholeheartedly taken in so much at once as a result of research, as for the propolis constituent containing said water extract or a supercritical extraction object, the health promotion effectiveness can be demonstrated very good. In addition, the component located in the boundary region which may be extracted with supercritical extraction and water hardly exists. Since a propolis original lump's (propolis raw material) permeability is furthermore easily raised in an operation of a hydrophilic organic solvent at this time, in being able to perform easily the process which obtains that extract, it is possible to cut down raw material expense easily.

[0049] - The synergistic effect by three kinds of extracts can be demonstrated very effectively to the supercritical extraction object 1 weight section by carrying out 0.5-6 weight section content of 1 - 20 weight section and the water extract for a hydrophilic organic solvent extract. Furthermore, the synergistic effect by three kinds of extracts can be demonstrated much more notably by exceeding 10 weight sections for hydrophilic organic solvent extract propolis, and carrying out 1-5 weight section content of the water extract propolis below 18 weight sections to the supercritical extraction propolis 1 weight section.

[0050] - The propolis constituent of this operation gestalt is constituted so that hydrophilic organic solvent extract powder, water extract powder, and supercritical extraction object powder may be contained. That is, since each extract powder extracted by three kinds of different extraction methods is alike, respectively and disintegration is carried out on the most extremely stable conditions, this propolis constituent may exist as a constituent which did not cause deterioration of each extract powder and was unified more. Furthermore, this propolis constituent can hold very high quality from a powder property being remarkably high for a long period of time. Furthermore, the outstanding salability can be given to a product from it being easy to change freely the mixing ratio which can expect the outstanding synergistic effect at this time.

[0051] - The propolis constituent granulation pharmaceutical preparation of an operation gestalt contains the above-mentioned propolis constituent, and contains hydrophilic organic solvent extract granulation, water extract granulation, and supercritical extraction object granulation. For this reason, since it has the same presentation as the above-mentioned propolis constituent, the synergistic effect by three kinds of extracts can be demonstrated very effectively. Furthermore, degradation of the physical properties by mixing of a different component is avoidable from it being granulation made to correspond to the physical properties of the extract for every extract, and in being able to prevent joining when a propolis constituent absorbs moisture effectively, the oil-soluble component in each extract can also prevent effectively the problem of dissociating at the time of mixing or preservation. Therefore, the propolis constituent granulation pharmaceutical preparation of very high quality can be offered by combining three kinds of extracts as granulation, respectively.

[0052] - When using a supercritical extraction object as granulation, it can manufacture easily by blending an antibonding agent 0.01-2 times by the weight ratio to the supercritical extraction object 1 beforehand. In the process which carries out disintegration of the supercritical extraction object of the shape of the shape of a paste, and emulsified liquid, separation of the oil content in a supercritical extraction object and generating of caking by adhesion of powder can be effectively prevented by using calcium as an antibonding agent especially.

[0053] In addition, it is possible by using the granulation of three kinds of said extracts as coating granulation, respectively to control the distributed stage and absorption stage to the inside of the body of each extract to arbitration. For this reason, while being able to promote further the absorption to the inside of the body of three kinds of extracts, the synergistic effect of the anti-inflammatory activity by three kinds of extracts can be heightened notably. The absorption and the synergistic effect to the inside of the body of each of said extract can be heightened remarkably notably by constituting the coating ratio of the coating granulation of a hydrophilic organic solvent extract, a water extract, and a supercritical extraction object especially, so that it may be set to 0.2 to 0.4, 0.4-0.6, and 0.05-0.2, respectively.

[0054] That is, in the absorption side of each extract, since a hydrophilic organic solvent extract is hydrophobicity, and distribution and the dissolution with the stomach are hard to be carried out, absorption within intestines tends to become slow. The water extract was in the condition of having diluted substantially with digestive juices when it shifted in an intestinal tract since it dissolved and distributed very promptly with the stomach, and since absorption within an intestinal tract was given to the concentration dependence target, the absorption coefficient suited the low inclination. Thus, when the absorption stage of three kinds of extracts did not gather, possibility that the additive effectiveness of each extract independent or two kinds of extracts will stop at being demonstrated, without the ability demonstrating sufficient synergistic effect was high. However, in the propolis constituent granulation pharmaceutical preparation containing the coating granulation of three kinds of extracts by which coating was carried out by said coating ratio, since the absorption stage to the inside of the body is appropriately controllable, the absorption stage of each extract is arranged and it becomes possible to carry out that it is easy to demonstrate those synergistic effects.

[Translation done.]

OPERATION

Although (edema depressant action) was demonstrated, it was checked that the propolis constituent (examples 1-4, an example 7, and example 8) which mixed three kinds of extracts demonstrates the anti-inflammation effectiveness heightened in multiplication. furthermore, the mixing ratio of an ethanol extract -- while increasing the content of flavonoids by raising a rate, when the organic acids and polysaccharide which are contained in a water extract auxiliary, and the hydrophobic high matter (fats-and-oils component etc.) contained in a supercritical extraction object are added, anti-inflammatory activity can be raised much more notably.

[0082] On the other hand, depressor effect with the propolis constituent granulation pharmaceutical preparation of an example 8 more expensive than the granulation pharmaceutical preparation of an example 7 was checked. It is guessed that this phenomenon is what is depended on the contact to the gastric acid of the active principle contained in them having been controlled, and condensation having been prevented, having come to distribute within intestines, and the absorbed amount having increased from coating of ethanol extract granulation and the supercritical extraction object granulation being carried out remarkably. Furthermore, by making the coating ratio of water extract granulation increase, and delaying a distributed stage, the active principle comes to be mostly absorbed with the absorption stage of an ethanol extract and a supercritical extraction object at a coincidence term, and while the absorption stage of the active principle in three kinds of extracts gathers, what is depended on the absorbed amount having increased is conjectured. Therefore, the synergistic effect by the active principle in three kinds of extracts is expected to be because for it to have been demonstrated very notably.

[0083] In addition, it changes as follows and each above-mentioned operation gestalt can also take shape.

- Constitute to carry out the water extract of the residue, and to carry out supercritical extraction of the residue further after performing a hydrophilic organic solvent extract previously using a propolis original lump. Or constitute to carry out supercritical extraction of the residue, and to carry out the water extract of the residue further after performing a hydrophilic organic solvent extract previously using a propolis original lump. Thus, when constituted, the raw material expense reduction effectiveness can be demonstrated still more effectively.

[0084] Furthermore, the technical thought which can be grasped from said operation gestalt is indicated below.

- Propolis constituent given in either of claim 1 to claims 4 characterized by setting the blending ratio of coal of said hydrophilic organic solvent extract propolis, water extract propolis, and supercritical extraction propolis to 2-15:0.6-5:1 by the weight ratio.

[0085] - Propolis constituent granulation pharmaceutical preparation according to claim 5 characterized by using the granulation of said supercritical extraction propolis as the coating granulation of the coating ratios 0.05-0.2 while using the granulation of said hydrophilic organic solvent extract propolis as the coating granulation of the coating ratios 0.2-0.4 and using the granulation of said water extract propolis as the coating granulation of the coating ratios 0.4-0.6. However, said coating ratio shows the rate of coating agent weight to coating granulation weight.

[0086] - The granulation of said supercritical extraction propolis is propolis constituent granulation pharmaceutical preparation according to claim 5 characterized by blending and carrying out disintegration 0.01-2 at a weight ratio about an antibonding agent to the supercritical extraction propolis 1.

[0087] - Health food pharmaceutical preparation characterized by containing the propolis constituent of a publication in either of claim 1 to claims 4. Thus, when constituted, the health food pharmaceutical preparation which can demonstrate efficacy high as health food and cosmetics can be offered cheaply efficiently.

[0088] - Cosmetics pharmaceutical preparation characterized by containing the propolis constituent of a publication in either of claim 1 to claims 4. Thus, when constituted, the cosmetics pharmaceutical preparation which can demonstrate efficacy high as health food and cosmetics can be offered cheaply efficiently.

[0089] - Health food pharmaceutical preparation characterized by containing propolis constituent granulation according to claim 5. Thus, when constituted, while being able to demonstrate efficacy high as health food and cosmetics, the health food excellent in stability can be offered.

[0090] - At least one sort which is a propolis constituent containing hydrophilic organic solvent extract propolis, water extract propolis, and supercritical extraction propolis, and is chosen from said water extract propolis and supercritical extraction propolis is a propolis constituent characterized by being extracted from the residue after a hydrophilic organic solvent extracts a propolis original lump. Thus, when constituted, efficacy high as health food and a cosmetics raw material can be demonstrated.

[Translation done.]

* NOTICES *

1.This document has been translated by computer. So the translation may not reflect the original precisely.
2.**** shows the word which can not be translated.
3.In the drawings, any words are not translated.

EXAMPLE

[Example] Hereafter, the example and the example of a comparison which materialized said operation gestalt are explained.
(Example 1 of a comparison) After the grinder (Ishizaki Electrical machinery Factory ********) ground 6kg of propolis original lumps from Brazil, 30l. of 95 capacity % ethanol was added, and the stirring extract was carried out at the room temperature for 24 hours. Next, 27kg (8.9 % of the weight of solid content) of ethanol extracts of propolis was obtained by filtering the extract containing said propolis grinding object through a filter paper (No.2 [ADVANTEC Oriental]), and removing residue. Vacuum concentration of the obtained extract was carried out until it became 20% of the weight in the evaporator, and 12kg of ethanol extracts was obtained. Furthermore, concentration hardening by drying of the 3kg of this ethanol extract was carried out by reduced pressure, and 600g of ethanol extracts was obtained. It considered as ethanol extract powder by grinding this ethanol extract with a mortar.
[0056] (Example 2 of a comparison) 2kg of propolis residue after the ethanol extract obtained in the example 1 of a comparison was measured by solid content conversion, 20l. of water was added, and the stirring extract was carried out at 45 degrees C for 5 hours. Next, the extract containing said propolis residue was rough-filtered until the moisture of residue was lost with the cloth for rough filtration (polyester gray yarn textiles), and 19.0kg of rough filtrate was obtained. After adding and stirring 340g (silica 100F made from Central Silica) of diatomaceous earth to this rough filtrate, 18.7kg of filtrate was obtained by filtering again using a filter paper (No.2 [ADVANTEC Oriental]). Vacuum concentration of this filtrate was carried out until it became 20% of the weight in the evaporator, and 1.1kg of water extracts was obtained. 0.6kg of this water extract was freeze-dried using the freezing vacuum dryer. 120g of water extract powder was obtained by grinding the obtained freeze-drying object.
[0057] (Example 3 of a comparison) 1kg of propolis residue after the ethanol extract obtained in the example 1 of a comparison was measured by solid content conversion, and the supercritical fluid processor (Mitsubishi Kakoki Kaisha, Ltd. make) performed supercritical fluid processing for 2 hours. In addition, it extracted on conditions with the flow rate of 5kg/hour, an atmospheric pressure [maximum-pressure 345] (35.0MPa), and a temperature of 40 degrees C at this time, using a carbon dioxide as supercritical gas. 59.3g of supercritical extraction objects was obtained by mixing an extract to homogeneity.
[0058] (Example 4 of a comparison) After the grinder (********) ground 2kg of propolis original lumps from Brazil, 20l. of water was added and the stirring extract was carried out at 45 degrees C for 5 hours. Next, the extract containing said propolis grinding object was rough-filtered until the moisture of residue was lost with the cloth for rough filtration (polyester gray yarn textiles), and 17.0kg of rough filtrate was obtained. After adding and stirring 340g (silica 100F made from Central Silica) of diatomaceous earth to this rough filtrate, 16.5kg of filtrate was obtained by filtering again using a filter paper (No.2 [ADVANTEC Oriental]). Vacuum concentration of this filtrate was carried out until it became 20% of the weight in the evaporator, and 1.4kg of water extracts was obtained. 0.7kg of this water extract was freeze-dried using the freezing vacuum dryer. 140g of water extract powder was obtained by grinding the obtained freeze-drying object.
[0059] (Example 5 of a comparison) After the grinder (********) ground 1kg of propolis original lumps from Brazil, the supercritical fluid processor (Mitsubishi Kakoki Kaisha, Ltd. make) performed supercritical fluid processing for 2 hours. In addition, it extracted on conditions with the flow rate of 5kg/hour, an atmospheric pressure [maximum-pressure 345] (35.0MPa), and a temperature of 40 degrees C at this time, using a carbon dioxide as supercritical gas. 98.3g of supercritical extraction objects was obtained by mixing an extract to homogeneity.
[0060] (Example 1) 1.0g of supercritical extraction objects obtained in the example 3 of a comparison was mixed with 10.7g of ethanol extract powder obtained in the example 1 of a comparison, and 1.3g of water extract powder obtained in the example 2 of a comparison, and 13.0g of propolis constituents was obtained.
[0061] (Example 2) 1.0g of supercritical extraction objects obtained in the example 3 of a comparison was mixed with 12.0g of ethanol extract powder obtained in the example 1 of a comparison, and 4.5g of water extract powder obtained in the example 2 of a comparison, and 17.5g of propolis constituents was obtained.
[0062] (Example 3) 1.0g of supercritical extraction objects obtained in the example 3 of a comparison was mixed with 17.0g of ethanol extract powder obtained in the example 1 of a comparison, and 3.0g of water extract powder obtained in the example 2 of a comparison, and 21.0g of propolis constituents was obtained.
[0063] (Example 4) 1.0g of supercritical extraction objects obtained in the example 3 of a comparison was mixed with 5.0g of ethanol extract powder obtained in the example 1 of a comparison, and 3.0g of water extract powder obtained in the example 2 of a comparison, and 9.0g of propolis constituents was obtained.
[0064] (Example 5) 1.0g of supercritical extraction objects obtained in the example 5 of a comparison was mixed with 10.7g of ethanol extract powder obtained in the example 1 of a comparison, and 1.3g of water extract powder obtained in the example 4 of a comparison, and 13.0g of propolis constituents was obtained.
[0065] (Example 6) 1.0g of supercritical extraction objects obtained in the example 5 of a comparison was mixed with 12.0g of ethanol extract powder obtained in the example 1 of a comparison, and 4.5g of water extract powder obtained in the example 4 of a comparison, and 17.5g of propolis constituents was obtained.
[0066] The radical prehension ability trial compared the active oxygen elimination operation which is a bioactive operation important as <radical prehension ability trial> health food pharmaceutical preparation and cosmetics pharmaceutical preparation.
[0067] The sample solution which dissolved respectively the class product of the examples 1-5 of a comparison and examples 1-6 by 0.001% of the weight of concentration into dehydrated ethanol was prepared. After adding 2ml of DPPH (1 and 1-diphenyl-2-picrylhydrazyl) dehydrated ethanol solutions of 60microM to 2ml of each sample solution, mixing to it and preparing the DPPH ethanol sample solution to it, it was made to react to it for 20 minutes at a room temperature. Then, the absorbance in the

wavelength of 517nm of each DPPH ethanol sample solution was measured using the spectrophotometer (PERKIN ELMER UV Spectrometer Lambda40). Moreover, after performing this actuation, using water as contrast, the purple clearance capacity (rate of radical prehension (%)) of each DPPH ethanol sample solution was calculated by having made the absorbance at that time into 100%. In addition, it is shown that antioxidation activity is so high that the value of this rate of radical prehension is high. A result is shown in a table 1.

[0068]

[A table 1]

検体名	含有量（%）			ﾗｼﾞｶﾙ捕捉率（%）	阻害濃度 IC_{50}（重量%）	白血球貪食率（%）
	ｴﾀﾉｰﾙ抽出	水抽出	超臨界抽出			
比較例1	100	—	—	35.6	0.0030	120.2
比較例2	—	100	—	24.2	0.0029	125.5
比較例3	—	—	100	26.8	0.0033	120.0
比較例4	—	100	—	20.5	0.0030	—
比較例5	—	—	100	23.8	0.0035	—
実施例1	82.3	10.0	7.7	60.5	0.0010	163.9
実施例2	68.6	25.7	5.7	52.3	0.0012	154.2
実施例3	81.0	14.3	4.7	53.1	0.0011	155.3
実施例4	55.6	33.3	11.1	40.2	0.0015	135.8
実施例5	82.3	10.0	7.7	48.0	0.0015	—
実施例6	68.6	25.7	5.7	46.4	0.0015	—

Consequently, it was checked that the propolis constituent of the examples 1-6 containing three kinds of extracts has notably high antioxidation activity as compared with the constituent of the examples 1-5 of a comparison. Especially, it was checked that an active oxygen elimination operation of the propolis constituent of examples 1-3 is more high as compared with examples 4-6.

[0069] Carrying out the measurement comparison of the strength of the activity which checks the hyaluronidase operation which is one of the mechanisms of a <hyaluronidase inhibition activity trial> allergy manifestation compared the antiallergic operation.

[0070] The sample solution which dissolved respectively the class product of the examples 1-5 of a comparison and examples 1-6 in the 0.1M acetic-acid buffer solution (pH3.5) by 0.001 - 0.1% of the weight of various concentration was prepared. Next, hyaluronidase is poured distributively 0.125ml (1100 units (U)) every beforehand, and said each sample solution is added into the solution which kept it warm for 20 minutes at 37 degrees C, and it warmed for 20 minutes and was made to react at 37 more degrees C. Then, the acetic-acid buffer solution containing a hyaluronic acid potassium (1.5mg/(ml)) was added, and it was made to react for 40 minutes at 37 degrees C. It was made to color after a reaction halt, the absorbance in 585nm of each sample (sample) was measured, and it asked for the rate of hyaluronidase activity inhibition (%) by the formula with the one following. Moreover, this actuation was performed using the 0.1M acetic-acid buffer solution as contrast, and it considered as control.

[0071]

[Equation 1]

$$\text{阻害率} = \frac{(\text{コントロールの吸光度}) - (\text{サンプルの吸光度})}{(\text{コントロールの吸光度})} \times 100$$

Furthermore, it asked for the concentration IC 50 (% of the weight) which checks the hyaluronidase activity of control 50% using the value of the rate of hyaluronidase activity inhibition computed by the sample solution of said various concentration. A result is shown in the above-mentioned table 1. Consequently, it was checked that the propolis constituent of the examples 1-6 containing three kinds of extracts has the remarkable high inhibition effectiveness to hyaluronidase as compared with the constituent of the examples 1-5 of a comparison. Especially, it was checked that the propolis constituent of examples 1-3 has higher effectiveness as compared with examples 4-6.

[0072] In order to examine phagocytic activity of leukocyte as an index of a <phagocytic-activity-of-leukocyte trial> immunity activation operation, it examined about the phagocytic activity facilitatory effect of the rat leucocyte to the yeast fungus which became extinct. The sample solution which dissolved the constituent of the examples 1-3 of a comparison and examples 1-4 in dimethyl sulfoxide (DMSO) as a sample so that it might become 110microg [/ml] concentration, respectively was used. Moreover, the contrast sample solution was prepared similarly, using Krestin powder (product made from Sankyo Pharmaceuticals) as positive control.

[0073] First, glycogen was prescribed for the patient into the abdominal cavity of a Wistar system rat (before or after the weight of 220g). Blood removal **** of the rat was carried out 4 hours after, and after pouring in the physiological saline into **** and washing intraperitoneal, said penetrant removers were collected with the leucocyte which exists in intraperitoneal. After the phosphate buffer solution's (PBS's) having washed this penetrant remover twice and performing a cel count, cell suspension was prepared so that it might become 5x106 cell [/ml] concentration. Moreover, after making yeast extinction fungus liquid YEAST (Bakers yeast) TypeII (SIGMA company make) suspend in PBS beforehand so that it may become 0.2 capacity %, 0.1ml of rat blood serums was added, and the yeast extinction bacillus solution was prepared by carrying out autoclave sterilization processing for 15 minutes at 121 degrees C.

[0074] Next, 0.04ml of each sample solution was added to 0.2ml of said cell suspension, 0.1ml of said yeast extinction bacillus solutions was added to each reaction mixture which incubated for 10 minutes at the room temperature, and it incubated for 30 minutes at 37 degrees C. After cooling, it dissolved at 95 capacity % ethanol so that it might become about the basic fuchsin at 1% of the weight, and 0.05ml of Fuchsine stain solutions prepared by filtering with a 0.45-micrometer filter was added, and they were dyed. Moreover, this actuation was performed, using PBS as contrast. The number of cells (white blood cell count which carried out phagocytosis of the yeast fungus) finally dyed with the number of cells (white blood cell count which did not carry out phagocytosis of the yeast fungus) and Fuchsine stain solution which were not dyed with said Fuchsine stain solution was counted, and it asked for the rate of the number of cells which carried out phagocytosis of the yeast fungus to the rate of

leucocyte phagocytosis (%), i.e., a total cell count. A result is shown in the above-mentioned table 1.
[0075] Consequently, as compared with the constituent of the examples 1-3 of a comparison, high leucocyte phagocytosis was demonstrated and, as for the propolis constituent of the examples 1-4 containing three kinds of extracts, the immunity activation operation was checked. It was checked that especially the phagocytic activity of leukocyte of the propolis constituent of examples 1-3 is very high. In addition, the rate of leucocyte phagocytosis of the Krestin powder as positive control was 150.4%.
[0076] (Example 7) It sprayed gradually, drying 250g of ethanol extracts of the example 1 of a comparison by the dried air using centrifugal floating mold coating granulator (Freund Industrial make) into 100g (non PARERU -101: trademark registration) of raw material granulation which consists of purified sucrose and corn starch under engine-speed 200r.p.m. and 80-degree C conditions. Corn-starch 210g was added gradually simultaneously, and 299g of ethanol extract granulation which made an ethanol extract and corn starch adhere to said raw material granulation front face was obtained.
[0077] Moreover, 67.5g of water extracts of the example 2 of a comparison was gradually sprayed on 100g of this raw material granulation on these conditions, drying at a dried air so that the temperature of goods may not exceed 50 degrees C. Corn-starch 12.5g was added gradually simultaneously, and 113.5g of water extract granulation which made a water extract and corn starch adhere to a raw material granulation front face was obtained. Moreover, under engine-speed 180r.p.m. and a room temperature, into 100g of raw material granulation, spraying 37.5g of 60% of the weight of corn-starch suspension, 75g [of supercritical extraction objects of the example 3 of a comparison] and corn-starch 57.5g beforehand used as content powder 17% of the weight was added gradually, it dried and 223.5g of supercritical extraction object granulation was obtained.
[0078] In addition, disintegration of said supercritical extraction object was performed as follows. After having mixed 20g of egg shell calcium in 25g of supercritical extraction objects of the example 3 of a comparison, mixing pineapple flow 55g further and considering as powder, 50g corn starch was mixed and 150g of content supercritical extraction object powder was produced 17% of the weight. Finally, 77.0g (10.7g as an ethanol extract) of said ethanol extract granulation, and 12.1g (1.3g as a water extract) of water extract granulation and 20g (1g as a supercritical extraction object) of supercritical extraction object granulation were mixed, and it considered as propolis constituent granulation pharmaceutical preparation.
[0079] (Example 8) Into 75g of ethanol extract granulation of an example 7, corn-starch 32.15g was added as a coating agent (coating), and 107.15g of coating granulation of an ethanol extract was obtained into it. In addition, the coating ratio of this granulation is 0.3. Moreover, corn-starch 50g was added as a coating agent into 50g of water extract granulation of an example 7, and 100g (a coating ratio is 0.5) of coating granulation of a water extract was obtained into it. Moreover, corn-starch 11.2g was added as a coating agent into 100g of supercritical extraction object granulation of an example 7, and 111.2g (a coating ratio is 0.10) of coating granulation of a supercritical extraction object was obtained into it. Finally, 110.2g (10.7g as an ethanol extract) of coating granulation of said ethanol extract, 24.1g (1.3g as a water extract) of coating granulation of a water extract, and 22.2g (1g as a supercritical extraction object) of coating granulation of a supercritical extraction object were mixed, and it considered as propolis constituent granulation pharmaceutical preparation.
[0080] In order to consider the edema depressant action used as the index of <edema inhibition test> anti-inflammatory activity, the acute inflammation model rat was produced, and it examined about the inflammation depressor effect. First, the day fast of the Wistar system rat (before or after the weight of 220g) was carried out, subcutaneous injection of the 0.1ml of the carrageenin solutions was carried out to the right rear crotch planta 1% of the weight, and the volume of a guide peg was measured 4 hours after. As a sample, the class product of the examples 1-3 of a comparison, examples 1-4, an example 7, and an example 8 was dissolved into 10% gum arabic solution, and it adjusted so that propolis (extract) concentration might become [ml] in 20mg /. 1 hour before carrageenin administration of each sample solution, 5 hours ago, the 3-hour front stirrup was administered orally so that it might be set to 200 mg/kg / 10ml, respectively. Moreover, sterilized water was used as contrast. And it asked for the rate of carrageenin edema control (%) from the measurement result of the volume of the guide peg of a rat. A result is shown in a table 2.
[0081]
[A table 2]

検体名	カラゲニン浮腫抑制率（%）			
	1時間前投与	3時間前投与	5時間前投与	平均
比較例1	3．4	38．2	30．2	23．9
比較例2	25．0	10．2	9．0	14．7
比較例3	5．3	44．2	15．6	21．7
実施例1	4．3	69．0	40．2	37．8
実施例2	13．2	55．7	33．6	34．1
実施例3	8．5	63．4	38．3	36．7
実施例4	15．6	40．5	29．1	28．4
実施例7	4．7	67．4	40．2	37．4
実施例8	3．4	66．3	50．8	40．2

Consequently, in the group which prescribed the propolis constituent granulation pharmaceutical preparation of the examples 1-4 containing three kinds of extracts, an example 7, and an example 8 for the patient 3 hours before carrageenin administration as compared with the constituent of the examples 1-3 of a comparison, remarkable high depressor effect was checked to the edema by acute inflammation. Each extract (constituent of the examples 1-3 of a comparison) is anti-inflammatory activity, respectively.

[Translation done.]

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(71)出願人　591045471
アピ株式会社
岐阜県岐阜市加納桜田町１丁目１番地

(71)出願人　598162665
株式会社山田養蜂場
岡山県苫田郡鏡野町市場194番地

(72)発明者　小川　一章
岐阜市加納桜田町１丁目１番地　アピ　株式会社内

(74)代理人　100068755
弁理士　恩田　博宣　（外１名）

最終頁に続く

(54)【発明の名称】プロポリス組成物及びその顆粒製剤

(57)【要約】
【課題】　健康食品及び化粧品素材として高い効能を発揮することができるように構成されたプロポリス組成物及びその顆粒製剤を提供する。
【解決手段】　プロポリス組成物は、親水性有機溶媒抽出プロポリス、水抽出プロポリス及び超臨界抽出プロポリスを含有するとともに、超臨界抽出プロポリス１重量部に対して親水性有機溶媒抽出プロポリスを１～２０重量部及び水抽出プロポリスを０．５～６重量部含有する。水抽出プロポリス及び超臨界抽出プロポリスは、プロポリス原塊を親水性有機溶媒で抽出した後の残渣より抽出されたものであるのが好ましい。このプロポリス組成物は、親水性有機溶媒抽出物粉末と、水抽出物粉末と、超臨界抽出物粉末とを含有するように構成するのが好ましい。プロポリス組成物顆粒製剤は、プロポリス組成物を含有するものであって、親水性有機溶媒抽出物顆粒と、水抽出物顆粒と、超臨界抽出物顆粒とを含有する。

1

【特許請求の範囲】

【請求項１】　親水性有機溶媒抽出プロポリスと、水抽出プロポリスと、超臨界抽出プロポリスとを含有するプロポリス組成物であって、

超臨界抽出プロポリス１重量部に対して、親水性有機溶媒抽出プロポリスを１～２０重量部、及び水抽出プロポリスを０．５～６重量部含有することを特徴とするプロポリス組成物。

【請求項２】　前記水抽出プロポリス及び超臨界抽出プロポリスから選ばれる少なくとも１種は、プロポリス原塊を親水性有機溶媒で抽出した後の残渣より抽出されたものであることを特徴とする請求項１に記載のプロポリス組成物。

【請求項３】　超臨界抽出プロポリス１重量部に対して、親水性有機溶媒抽出プロポリスを１０重量部を越え、かつ１８重量部以下、及び水抽出プロポリスを１～５重量部含有することを特徴とする請求項１又は請求項２に記載のプロポリス組成物。

【請求項４】　前記親水性有機溶媒抽出プロポリスを粉末化した親水性有機溶媒抽出物粉末と、前記水抽出プロポリスを粉末化した水抽出物粉末と、前記超臨界抽出プロポリスを粉末化した超臨界抽出物粉末とを含有することを特徴とする請求項１から請求項３のいずれかに記載のプロポリス組成物。

【請求項５】　請求項１から請求項４のいずれかに記載のプロポリス組成物を含有するプロポリス組成物顆粒製剤であって、

前記親水性有機溶媒抽出プロポリスを顆粒状に造粒した親水性有機溶媒抽出物顆粒と、前記水抽出プロポリスを顆粒状に造粒した水抽出物顆粒と、前記超臨界抽出プロポリスを顆粒状に造粒した超臨界抽出物顆粒とを含有することを特徴とするプロポリス組成物顆粒製剤。

【発明の詳細な説明】

【０００１】

【発明の属する技術分野】この発明は、健康食品製剤や美容製剤等として利用されるプロポリス組成物、及びその組成物を含有するプロポリス組成物顆粒製剤に関するものである。

【０００２】

【従来の技術】プロポリス（プロポリス原塊）は蜂ヤニともいわれ、セイヨウミツバチの巣の巣壁を構成する樹脂状ないしは蝋状の物質である。このプロポリスは、ミツバチが周辺の植物から採取してきた樹液や植物体であってしばしば蜜蝋や花粉が混入されており、一般に茶褐色ないし黒褐色を呈し、多種多様な成分を含有している。

【０００３】このプロポリスは、ヨーロッパにおいては医薬品或いは健康食品の素材として古くから用いられてきたが、近年日本においても健康食品や化粧品の素材として多くの製品に使用されるようになった。プロポリス

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の主要な生理活性としては、活性酸素消去能及び免疫賦活作用が知られており、健康食品の素材としての効能を裏付けている。また、消炎作用や鎮痛作用、抗アレルギー作用や広い範囲の病原菌に対する抗菌作用も知られている。中でも著しい抗癌・抗腫瘍作用があることが学会において報告され、複数の新しい殺癌物質が成分中から発見報告されたことからプロポリスの優れた効能が一躍世の注目を集めることとなった。

【０００４】このプロポリス中に含まれる化学成分としては、極性の高い有機酸化合物からフラボノイド類、ポリフェノール類等さらには極性の低いテルペノイド類等非常に多くの化合物が確認されている。これらの物質の生理活性が複雑に作用しあってプロポリスの優れた生理活性を形成しているものと考えられる。

【０００５】プロポリス原塊は、そのままの状態で摂取するのは極めて困難であることから、エタノール等の親水性有機溶媒又は水で抽出された抽出物として摂取されるのが一般的である。このプロポリスの親水性有機溶媒抽出物又は水抽出物には、種々の生理活性物質が含有されており、健康食品分野においてその薬理作用を利用した様々な製品が市販されている。また、特開２０００－３２５０３２号公報では、アルコール抽出プロポリスに水抽出プロポリスを徐々に添加・混合することにより、アルコール抽出プロポリス特有の樹脂成分を沈澱濾過して取り除いたプロポリス製品について開示されている。そして、このプロポリス製品は、アルコール抽出プロポリス及び水抽出プロポリスの夫々が有する難点を克服するとともに、単独の溶媒（アルコール又は水）で抽出されたプロポリス抽出物と比較して、夫々の成分の相乗効果が期待できるうえ飲用に適しているとしている。

【０００６】

【発明が解決しようとする課題】ところが、前記従来のアルコール抽出プロポリスと水抽出プロポリスを含有するプロポリス製品では、プロポリス原塊中の成分のうち、アルコールに可溶な成分と水に可溶な成分のみしか含有されておらず、しかも沈澱濾過工程において樹脂成分を除去することで多くの有効成分を失っていて、プロポリス有効成分の一部しか摂取することができなかった。このため、前記相乗効果は、プロポリス原塊をまるごと摂取したときの多数の有効成分による生理活性の相乗効果と比べると、著しく低いものに過ぎなかった。

【０００７】この発明は、上記のような従来技術に存在する問題点に着目してなされたものである。その目的とするところは、健康食品及び化粧品素材として高い効能を発揮することができるように構成されたプロポリス組成物及びその顆粒製剤を提供することにある。

【０００８】

【課題を解決するための手段】上記の目的を達成するために、請求項１に記載の発明のプロポリス組成物は、親水性有機溶媒抽出プロポリスと、水抽出プロポリスと、

超臨界抽出プロポリスとを含有するプロポリス組成物であって、超臨界抽出プロポリス１重量部に対して、親水性有機溶媒抽出プロポリスを１～２０重量部、及び水抽出プロポリスを０．５～６重量部含有することを特徴とするものである。

【０００９】請求項２に記載の発明のプロポリス組成物は、請求項１に記載の発明において、前記水抽出プロポリス及び超臨界抽出プロポリスから選ばれる少なくとも１種は、プロポリス原塊を親水性有機溶媒で抽出した後の残渣より抽出されたものであることを特徴とするものである。

【００１０】請求項３に記載の発明のプロポリス組成物は、請求項１又は請求項２に記載の発明において、超臨界抽出プロポリス１重量部に対して、親水性有機溶媒抽出プロポリスを１０重量部を越え、かつ１８重量部以下、及び水抽出プロポリスを１～５重量部含有することを特徴とするものである。

【００１１】請求項４に記載の発明のプロポリス組成物は、請求項１から請求項３のいずれかに記載の発明において、前記親水性有機溶媒抽出プロポリスを粉末化した親水性有機溶媒抽出物粉末と、前記水抽出プロポリスを粉末化した水抽出物粉末と、前記超臨界抽出プロポリスを粉末化した超臨界抽出物粉末とを含有することを特徴とするものである。

【００１２】請求項５に記載の発明のプロポリス組成物顆粒製剤は、請求項１から請求項４のいずれかに記載のプロポリス組成物を含有するプロポリス組成物顆粒製剤であって、前記親水性有機溶媒抽出プロポリスを顆粒状に造粒した親水性有機溶媒抽出物顆粒と、前記水抽出プロポリスを顆粒状に造粒した水抽出物顆粒と、前記超臨界抽出プロポリスを顆粒状に造粒した超臨界抽出物顆粒とを含有することを特徴とするものである。

【００１３】

【発明の実施の形態】以下、この発明を具体化した実施形態を詳細に説明する。実施形態のプロポリス組成物は、親水性有機溶媒抽出プロポリス（以下、親水性有機溶媒抽出物と記載する）と、水抽出プロポリス（以下、水抽出物と記載する）と、超臨界抽出プロポリス（以下、超臨界抽出物と記載する）とを含有するものである。このプロポリス組成物は、健康食品製剤や美容製剤等の種々の製剤の形態で、経口又は経皮投与されて利用される。このプロポリス組成物は、異なる抽出方法による３種類の抽出物に含まれる有効成分の相乗効果によって、極めて高い健康増進作用と美容効果が発揮される。前記健康増進作用及び美容効果は、浮腫抑制活性、ヒアルロニダーゼ阻害活性、白血球貪食促進活性及び活性酸素消去能の指標となるラジカル捕捉促進活性を測定比較することで推定、確認される。

【００１４】各抽出物を抽出するための出発原料（以下、プロポリス原料と記載する）は、それぞれ別個のプロポリス原塊を３種類準備して３種類の抽出操作に用いることが可能である。しかしながら、抽出工程の作業性及び有効成分の回収率（経済性）を考慮すると、プロポリス原塊を２種類以上の抽出操作により抽出するように構成するのが好ましい。すなわち、プロポリス原塊をまず親水性有機溶媒で抽出した後、その残分（親水性有機溶媒に不溶性の残渣）を水抽出又は超臨界抽出に供しても良いし、逆に超臨界抽出を行った後の残分を親水性有機溶媒抽出又は水抽出に供してもよい。

【００１５】最も好ましくは、プロポリス原塊を用いて先に親水性有機溶媒抽出を行った後、その残分（残渣）を水抽出又は超臨界抽出するように構成するとよい。このとき、水及び親水性有機溶媒で抽出され得る境界域に位置する親水性成分、又は超臨界抽出及び親水性有機溶媒で抽出され得る境界域に位置する疎水性成分がプロポリス組成物中に重複して含有されることがないことから、健康増進効果等に対する抑制効果を低減させることが容易である。すなわち、前記親水性成分又は疎水性成分を一度に多量に摂取すると、かえって健康増進を抑制する働きがある。また、先に親水性有機溶媒抽出に供した後の残分は、親水性有機溶媒の作用で浸透性が良好になっていることから、その後の水抽出又は超臨界抽出においての収率を容易に向上させることができる。

【００１６】なお、前記プロポリス原塊は、ブラジル、中国、日本、米国、ヨーロッパ等のいずれの産地のものも使用可能であるが、水抽出においては抽出収率の高いブラジル産を使用するのが特に好ましい。

【００１７】親水性有機溶媒抽出物は、抽出溶媒として親水性有機溶媒又はその水希釈液を用いて、プロポリス原料中の親水性有機溶媒に可溶な成分を抽出することによって得られるが、健康食品としての組成物の製造には親水性有機溶媒としてはエタノールを用いることが好ましい。この親水性有機溶媒抽出物には、フラボノイド類、ポリフェノール類、有機酸類、テルペノイド類等の種々の有効成分が含まれており、活性酸素消去作用、免疫賦活作用、消炎作用、抗癌作用等の健康増進作用を発揮する。

【００１８】前記親水性有機溶媒は、水に溶解する性質を有するエタノール、メタノール、イソプロパノール等の低級アルコールのほか、アセトンやメチルエチルケトン等のケトン類が適宜選択して使用することができるが、溶媒の性質及びプロポリス組成物を食品として経口することを考えればエタノールが最も好ましい。親水性有機溶媒としてエタノールを用いるときその濃度は、好ましくは６０～１００容量％、より好ましくは８０～１００容量％である。この濃度が６０容量％未満の場合には、エタノールに可溶な有効成分を本実施形態の構成に適した比率でかつ効率良く抽出することができない。エタノールの使用量は、プロポリス原料に対して好ましくは１～２０倍量、より好ましくは２～１０倍量、さらに

好ましくは３～８倍量である。この使用量が１倍量未満の場合には、有効成分の収率が低下する。逆に２０倍量を超える場合には、装置が不必要に大きくなるばかりでなく濃縮等の工程に時間がかかり作業性が著しく低下する。

【００１９】抽出温度は１０～３０℃の常温付近の温度でよく、その抽出温度で撹拌しながら２４時間以上抽出操作を行うとよい。なお、前記抽出温度が１０℃未満の場合には、有効成分の収率が低下する。逆に３０℃を超える場合には、抽出後の濾過性が悪くなって作業性が低下する。そして、上記の抽出条件で有効成分を充分に抽出した後、濾紙濾過又は珪藻土濾過を行うことにより親水性有機溶媒抽出物液を得る。この親水性有機溶媒抽出物液の溶媒を蒸発し乾燥することで親水性有機溶媒抽出物が得られる。この親水性有機溶媒抽出物は、褐色ないし黒褐色の樹脂状固体で、これを粉砕すれば純粋の親水性有機溶媒抽出物粉末が得られるが、粉末物性が劣るので、前記親水性有機溶媒抽出物液を、必要に応じて希釈、濃縮した後、乳糖やデキストリン等の賦形剤を添加して乾燥し、粉末化して親水性有機溶媒抽出物粉末としてもよい。

【００２０】水抽出物は、抽出溶媒として水を用いて、プロポリス原料中の水に可溶な成分を抽出することによって得られる。この水抽出物には、有機酸類、多糖類、蛋白質等の種々の有効成分が含まれており、抗酸化作用、ラジカル捕捉促進作用、ヒアルロニダーゼ阻害活性、抗癌作用等の健康増進作用を発揮する。抽出溶媒の使用量は、プロポリス原料に対して好ましくは１～２０倍量、より好ましくは２～１５倍量、さらに好ましくは５～１２倍量である。この抽出溶媒の使用量が１倍量未満の場合には、有効成分の収率が低下する。逆に２０倍量を超える場合には、濃縮等の工程に時間がかかり作業性が著しく低下する。

【００２１】抽出温度は、好ましくは２０～９０℃、より好ましくは３０～８０℃、さらに好ましくは４０～６０℃である。この抽出温度が２０℃未満の場合には、抽出工程に長時間を要し、品質の低下を招くばかりでなく有効成分の収率も低下する。逆に９０℃を越える場合には、有効成分の変性が起こり相乗効果が低下することが予想される。また、抽出時間は抽出溶媒の使用量にもよるが、充分な量の有効成分を抽出するために、２時間以上かけて抽出するのが望ましい。

【００２２】そして、上記の抽出条件で充分に有効成分を抽出した後、濾紙濾過又は珪藻土濾過を行うことによって水抽出物液を得る。さらに、必要に応じて、この水抽出物液を濃縮した後に凍結乾燥すれば、純粋な水抽出物凍結乾燥粉末が得られる。さらに物性のよい粉末を得るためには、前記の水抽出物液に乳糖やデキストリン等の賦形剤を添加した後に凍結乾燥して粉末特性に優れた水抽出物凍結乾燥粉末としてもよい。また、前記の純粋な水抽出物凍結乾燥粉末に乳糖やデキストリン等の賦形剤を添加しても粉末特性のよい水抽出物凍結乾燥粉末（以下、水抽出物粉末と記載する）が得られる。

【００２３】超臨界抽出物は、公知の超臨界流体抽出装置を用い、超臨界流体を臨界温度以上及び臨界圧力以上の条件下で超臨界状態にした超臨界流体とプロポリス原料とを接触させることにより、プロポリス原料から所定の成分を抽出したものである。超臨界流体として二酸化炭素を用いる場合は、３１．１℃の臨界温度以上及び７２．８気圧（７．４ＭＰａ）の臨界圧力以上として超臨界流体状態となった二酸化炭素によってプロポリス原料を抽出する。この二酸化炭素を用いた超臨界抽出物には、フラボノイド類、テルペノイド、その他の疎水性生理活性物質等が含まれており、ヒアルロニダーゼ阻害活性、抗癌作用、浮腫抑制作用等の健康増進作用を発揮することが確認されている。

【００２４】前記超臨界流体は、エタン、プロパン、二酸化炭素、亜酸化窒素等が使用可能であるが、二酸化炭素を用いるのが最も好ましい。この二酸化炭素は、臨界温度が常温に近いうえに極性がエタノールより低いという抽出対象化合物に適合する物理的、化学的性質を有している。二酸化炭素はこのように抽出工程での物性が優れているばかりでなく無味・無臭で超臨界抽出製品の味にも影響を及ぼさないことから本実施形態に用いる超臨界流体としては二酸化炭素が最も好ましい。

【００２５】超臨界流体抽出における操作には、超臨界流体が臨界点近傍において、わずかな温度差、圧力差に対して密度と溶解性が大きく変化する性質を利用するため処理の温度及び圧力には適切な上下幅が必要である。二酸化炭素を用いる場合の操作温度は、好ましくは３２～８０℃、より好ましくは３２～５０℃である。また、その操作圧力は、好ましくは７３～５００気圧（７．４～５０．７ＭＰａ）、より好ましくは７３～４００気圧（７．４～４０．５ＭＰａ）である。超臨界流体としての二酸化炭素の流量（流速）は、プロポリス原料１ｋｇに対して、好ましくは１～１０ｋｇ／時間、より好ましくは３～７ｋｇ／時間である。処理時間は、プロポリス原料の量や状態により異なるが、テスト又は処理実績から抽出が完了する時間を確認することで適宜に決定することが可能である。

【００２６】そして、上記の抽出条件で抽出されたプロポリスの超臨界抽出物の性状は、抽出の経過時間によっても変化する。多くはペースト状であるが一部は粉末ないし塊状の固体として得られることもある。エントレーナーとしてエタノールを用いるときは、エタノールを含んだ液状となる。超臨界抽出物は、抽出直後は抽出原料に含まれるエタノール、エントレーナーとしてのエタノール等が含まれるほか、断熱膨張で固体化した二酸化炭素が含まれる。さらに抽出経過時間によって異なる組成を持つ不均一な抽出物として得られるので、均一に撹拌

しながらエタノールと二酸化炭素を除去して固形の超臨界抽出物とした後、粉砕すれば純粋な超臨界抽出物粉末となる。さらによりよい粉末特性を与えるために、必要に応じて、超臨界抽出物に乳糖やデキストリン等の賦形剤を添加して粉末化した超臨界抽出物粉末としてもよい。

【００２７】本実施形態のプロポリス組成物中の親水性有機溶媒抽出物の配合割合は、超臨界抽出物１重量部に対して、好ましくは１～２０重量部、より好ましくは１０重量部を越え、かつ１８重量部以下である。超臨界抽出物１重量部に対して親水性有機溶媒抽出物の配合割合が１重量部未満の場合には、健康食品又は美容製剤としての充分な効能及び効果を発揮させることができない。逆に超臨界抽出物１重量部に対して親水性有機溶媒抽出物の配合割合が２０重量部を超える場合には、水抽出物に対する超臨界抽出物の含有量が相対的に低下することから、それら水抽出物と超臨界抽出物との相乗効果が充分に発揮されない。

【００２８】本実施形態のプロポリス組成物中の水抽出物の配合割合は、超臨界抽出物１重量部に対して、好ましくは０．５～６重量部、より好ましくは１～５重量部である。超臨界抽出物１重量部に対して水抽出物の配合割合が０．５重量部未満の場合には、健康食品又は美容製剤としての充分な効能及び効果を発揮させることができない。逆に超臨界抽出物１重量部に対して水抽出物の配合割合が６重量部を超える場合には、親水性有機溶媒抽出物に対する超臨界抽出物の含有量が相対的に低下することから、それら親水性有機溶媒抽出物と超臨界抽出物との相乗効果が充分に発揮されない。

【００２９】上記のように構成されるプロポリス組成物は、健康食品製剤や美容製剤等として経口又は経皮投与されて利用される。その際、このプロポリス組成物中には、上記有効成分の健康増進効果を損なわない範囲内で、例えば、デキストリン、シクロデキストリン、乳糖等の賦形剤、炭酸水素ナトリウム等の膨化剤、カルナバロウ、シェラック、ミツロウ等の光沢剤、ペクチンカルボキシメチルセルロース、カンテン、デンプン等のゲル化剤、アルギン酸、カラギナン、キサンタンガム、キトサン等の増粘剤、砂糖、蜂蜜、カンゾウ抽出物、ステビア、サッカリンナトリウム、オリゴ糖、エリスリトール、水飴、異性化糖等の甘味剤、キラヤ抽出物、レシチン、グリセリン、グリセリン脂肪酸エステル、大豆サポニン等の乳化剤、シナモン精油、ジャスミン精油、ローズマリー精油、ライム精油等の香味料、カラメル、アカキャベツ、クチナシ、ムラサキイモ、ブドウ、ウコン等の色素、乳酸、乳酸塩、クエン酸、リンゴ酸、炭酸ナトリウム等のｐＨ調整剤を添加してもよい。

【００３０】健康食品製剤としては、上記プロポリス組成物を食品素材、飲料品素材又は医薬品素材中に添加することによって、粉末状、液状、顆粒状、錠剤、カプセル状、スティック状等の形状に加工され、健康食品、健康飲料又は医薬部外品として使用される。医薬部外品としては、石鹸、歯磨き粉等に配合されて使用される。美容製剤としては、上記プロポリス組成物を食品素材、飲料品素材又は化粧品素材に添加することによって、液状、乳液状、半固形状、粉末状等の形状に加工され、美容食品、美容飲料又は化粧品として使用される。前記化粧品は、化粧の種類に応じて、アルコール類、油脂類界面活性剤、精製水等が適宜添加される。

【００３１】一方、このプロポリス組成物を経口剤として利用する場合には、錠剤、カプセル剤、顆粒、散剤、シロップ剤、ドリンク剤等の諸形態に加工される。錠剤及びカプセル剤に加工する場合には、結合剤、賦形剤、膨化剤、光沢剤、甘味剤、香味剤等が好適に添加される。錠剤は、シェラック又は砂糖で被覆することもできる。また、カプセル剤の場合には、上記の材料にさらに油脂等の液体担体を含有させることができる。一方、非経口剤として利用する場合には、軟膏剤、クリーム剤、水剤等の外用剤の形態で経皮投与されて使用される。この外用剤の基剤としては、ワセリン、パラフィン、油脂類、ラノリン、マクロゴール等が好適に用いられ、通常の方法によって軟膏剤やクリーム剤等とすることができる。

【００３２】一方、上記プロポリス組成物を粉末状、特に微小な粒子径の粉末状にした場合には、プロポリス組成物中の成分が吸湿等により保存中に固結する可能性が高いため、粒子径の大きな顆粒状の顆粒製剤とすることが望ましい。

【００３３】このプロポリス組成物を顆粒製剤とする場合には、３種類の抽出物を混合した後に粉末化し、造粒装置にて定法に従って顆粒状に成形して顆粒製剤とすることができる。或いは、造粒装置を用いて３種類の粉末化された抽出物を混合しながら顆粒状に造粒して顆粒製剤とすることもできる。或いは、コーティング造粒装置を用いて、精製白糖やトウモロコシデンプン等で予め顆粒状に造粒された原料顆粒の表面に、３種類の抽出物を混合した液体（液状のプロポリス組成物）を直接噴霧するか、又は３種類の粉末化された抽出物を糊剤を介して付着させながら混合し、その後乾燥させることによってプロポリス組成物顆粒製剤とすることも可能である。

【００３４】しかしながら、上記顆粒製剤の製造方法では、各抽出物の性質（脂溶性の強弱等）の相違により混合時又は保存時に分離等の問題が生じる可能性が高いことから、各抽出物毎に顆粒状にした後に所定の比率で混合することによって顆粒製剤とするのが最も好ましい。すなわち、まず、親水性有機溶媒抽出物顆粒、水抽出物顆粒及び超臨界抽出物顆粒をそれぞれ別々に造粒した後、３種類の顆粒を混合することにより顆粒製剤を製造するように構成するのが最も好ましい。

【００３５】親水性有機溶媒抽出物顆粒は、親水性有機

溶媒抽出物に乳糖やデキストリン等の賦形剤を添加することにより粉末化した後、造粒装置にて常法に従って顆粒状に造粒される。或いは、コーティング造粒装置を用いて、精製白糖やトウモロコシデンプン等で予め顆粒状に造粒された原料顆粒の表面に、液状の親水性有機溶媒抽出物を直接噴霧するか、又は粉末化された親水性有機溶媒抽出物を糊剤を介して付着させ、その後乾燥させることによって造粒することも可能である。この顆粒中に含まれる親水性有機溶媒抽出物の含有量は、固形分で５～５０重量％であるのが好ましい。この親水性有機溶媒抽出物の含有量が５重量％未満の場合には、プロポリス組成物顆粒製剤中に充分な量の有効成分を含有させることができない。逆に５０重量％を超える場合には、粉末化及び造粒工程が著しく困難になる。

【００３６】水抽出物顆粒は、上記親水性有機溶媒抽出物顆粒と同様の製造方法により顆粒とすることが可能であるが、フリーズドライ法により粉末化した後、造粒装置を用いて顆粒状にすることもできる。この水抽出物顆粒中に含まれる水抽出物の含有量は、上記親水性有機溶媒抽出物顆粒の場合と同様の理由で、固形分で５～５０重量％であるのが好ましい。

【００３７】超臨界抽出物顆粒は、前記親水性有機溶媒抽出物顆粒と同様の製造方法により顆粒とすることが可能である。さらに、この超臨界抽出物顆粒を製造する際には、予めペースト状又は乳化液状の超臨界抽出物を粉末化することが好ましい。この粉末化には前記賦形剤とともにカルシウムや二酸化ケイ素等の付着防止剤を添加して粉末化するように構成するのが好ましい。このとき、超臨界抽出物粉末中の超臨界抽出物の含有量は、好ましくは１０～３５重量％、より好ましくは１５～２５重量％である。この超臨界抽出物の含有量が１０重量％未満の場合には、プロポリス組成物顆粒製剤中に充分な量の有効成分を含有させることができない。逆に３５重量％を越える場合には、粉末化及び造粒工程が著しく困難になる。

【００３８】さらに、付着防止剤の配合割合は、超臨界抽出物１に対して重量比で好ましくは０．０１～２、より好ましくは０．０５～１である。この付着防止剤の重量比が０．０１未満の場合には、超臨界抽出物を粉末化する際に油分が分離したり、粉末同士の固結が生じたりする。逆に２を越える場合には、プロポリス特有の味及び匂いが弱まって商品の品質が損なわれる。これら３種類の抽出法ごとの顆粒を個別に用意して、それらを混合して本実施形態のプロポリス組成物とすることにより、超臨界抽出物中に多く含まれる油分の分離や、粉末同士の付着による固結の発生を効果的に防止することが可能である。

【００３９】また、この超臨界抽出物顆粒中に含まれる超臨界抽出物の含有量は、好ましくは３～３５重量％、より好ましくは５～２０重量％である。この超臨界抽出物の含有量が３重量％未満の場合には、プロポリス組成物顆粒製剤中に充分な量の有効成分を含有させることができない。逆に３５重量％を越える場合には、粉末化及び造粒工程が著しく困難になる。

【００４０】さらに、上記の様に各々造粒した親水性有機溶媒抽出物顆粒、水抽出物顆粒及び超臨界抽出物顆粒においては、造粒後の顆粒の表面にコーティング剤をコーティングすることによってコーティング顆粒とするのが好ましい。なお、前記コーティング剤としては、デキストリン又はコーンスターチが好適に用いられる。このとき、保存時における顆粒製剤同士又は顆粒同士の付着による品質低下を容易に防止することができるうえ、有効成分の体内への分散時期及び吸収時期を適宜コントロールすることが可能となる。特に、３種類の抽出物顆粒からなるプロポリス組成物顆粒製剤の場合には、有効成分の体内への吸収時期を各顆粒毎にコントロールすることができることから、３種類の抽出物の体内における生理活性発現のピークを揃えて相乗効果を顕著に高めることが可能となる。

【００４１】親水性有機溶媒抽出物のコーティング顆粒は、コーティング造粒装置を用いて、親水性有機溶媒抽出物顆粒の表面に、液状のコーティング剤を直接噴霧するか、又は粉末化されたコーティング剤を糊剤を介して付着させ、その後乾燥させることにより調製される。水抽出物のコーティング顆粒、超臨界抽出物のコーティング顆粒及び造粒前に３種類の抽出物を混合した後に造粒したプロポリス組成物顆粒製剤も同様に調製される。

【００４２】親水性有機溶媒抽出物のコーティング顆粒のコーティング比、すなわちコーティング顆粒の固形分重量に対するコーティング剤重量の比率（割合）は、０．２～０．４であるのが好ましい。このコーティング比が０．２未満の場合には、胃内での崩壊時間が短いために胃液にさらされる時間が長くなり、親水性有機溶媒抽出物中の成分が凝集しやすくなる。その結果、胆汁酸による乳化作用を受け難くなって体内への吸収率が低下する。逆に０．４を超える場合には、胃内で充分に崩壊されないことから有効成分の吸収が著しく遅れる傾向にある。

【００４３】水抽出物のコーティング顆粒のコーティング比は、０．４～０．６であるのが好ましい。このコーティング比が０．４未満の場合には、コーティング顆粒の表面付近に存在する水抽出物中の成分が吸湿し、コーティング顆粒同士の付着が起こるおそれがある。また、胃内において有機酸等の低分子物質が容易に溶出して希釈され、腸管の膜透過性が低下することにより体内への吸収率が低下するおそれもある。逆に０．６を超える場合には、有効成分の含有量が低下することから充分な抗炎症効果が発揮されない。

【００４４】超臨界抽出物のコーティング顆粒のコーティング比は、好ましくは０．０５～０．２、より好まし

くは０．０５～０．１である。このコーティング比が０．０５未満の場合には、胃内での崩壊時間が短いために胃液にさらされる時間が長くなり、超臨界抽出物中の成分が凝集しやすくなる。逆に０．２を超える場合には、胃内で充分に崩壊されずに有効成分の吸収が著しく遅れる傾向にある。

【００４５】上記実施形態によって発揮される効果について、以下に記載する。

・　実施形態のプロポリス組成物は、親水性有機溶媒抽出物と、水抽出物と、超臨界抽出物との３種類の抽出物を含有するものである。前記各抽出物は、それぞれ異なる抽出溶媒（抽出方法）により抽出されたものであることから、互いに異なる有効成分を含有している。このプロポリス組成物は、これら異なる有効成分の相乗効果により、１種類の抽出物又は２種類の抽出物の混合物と比較して、健康食品及び美容製剤としてのより高い効能と効果を発揮することができ、優れた健康食品及び美容製剤を得ることができる。

【００４６】さらに、このプロポリス組成物は、水溶性の物質、親油性の物質及びその中間の性質を有する物質が含有されていることから、プロポリス原塊に含まれる健康増進活性を有する多種類の生理活性物質であって抽出可能な物質を実質上すべてを含むと言うことができる。このため、プロポリス原塊をまるごと摂取するのと同様にプロポリス中のほとんどすべての生理活性物質を摂取できるばかりでなく、前記３種類の抽出物の組合わせ比率の組成物はプロポリス原塊そのものよりさらに高い効能を相乗効果として発揮し得るものである。

【００４７】一方、特開２００１－７８６８６号公報では、アルコール抽出プロポリスと水抽出プロポリスに超臨界抽出プロポリスを加えたプロポリス組成物調製の試みも行われている。しかしながら、この試みでは、均一な３種の抽出物からなる組成物を調製することのみを目的としており、有効成分の効能に相乗的な向上効果をもたらすことに関しては全く配慮が払われていない。さらに、生理活性物質（有効成分）にとっては極めて過酷な製造条件が採用されており、例えば熱に弱いとされる水抽出プロポリスを含む組成物の粉末化に、組成物の品温が高温化するスプレードライヤーが使用されている。このため、３種の抽出物による相乗効果が期待できないばかりでなく、かえって効能が減殺される可能性が高い。

【００４８】・　水抽出物又は超臨界抽出物として、プロポリス原塊を親水性有機溶媒で抽出した後の残渣より抽出されたものとすることによって、親水性有機溶媒で抽出される成分のうち、極度な親水性を有する親水性成分又は極度な疎水性を有する疎水性成分がプロポリス組成物中に重複して多量に含有されることがない。本発明者らによる鋭意研究の結果、これらの成分を一度に多量に摂取した場合には、健康増進効果等をかえって抑制する働きがあることが解明されたことから、前記水抽出物又は超臨界抽出物を含有するプロポリス組成物は、健康増進効果を極めて良好に発揮させることができる。なお、超臨界抽出及び水で抽出され得る境界域に位置する成分はほとんど存在しない。さらにこのとき、親水性有機溶媒の作用でプロポリス原塊（プロポリス原料）の浸透性が容易に高められることから、その抽出物を得る工程を容易に行うことができるうえ、原料費を容易に節約することが可能である。

【００４９】・　超臨界抽出物１重量部に対して、親水性有機溶媒抽出物を１～２０重量部、及び水抽出物を０．５～６重量部含有することによって、３種類の抽出物による相乗効果を極めて効果的に発揮させることができる。さらに、超臨界抽出プロポリス１重量部に対して、親水性有機溶媒抽出プロポリスを１０重量部を越え、かつ１８重量部以下、及び水抽出プロポリスを１～５重量部含有することによって、３種類の抽出物による相乗効果をより一層顕著に発揮させることができる。

【００５０】・　本実施形態のプロポリス組成物は、親水性有機溶媒抽出物粉末と、水抽出物粉末と、超臨界抽出物粉末とを含有するように構成されている。すなわち、このプロポリス組成物は、３種類の異なる抽出法により抽出された各抽出物粉末が、それぞれに最も安定性の高い条件で粉末化されていることから、各抽出物粉末の変質を来たすことがなく、より一体化した組成物として存在し得る。さらに、このプロポリス組成物は、粉末特性が著しく高いことから極めて高い品質を長期間保持することができる。さらにこのとき、優れた相乗効果が期待できる混合比を自由に変化させることが容易であることから、優れた商品性を製品に付与することができる。

【００５１】・　実施形態のプロポリス組成物顆粒製剤は、上記プロポリス組成物を含有するものであって、親水性有機溶媒抽出物顆粒と、水抽出物顆粒と、超臨界抽出物顆粒とを含有するものである。このため、上記プロポリス組成物と同じ組成を有することから、３種類の抽出物による相乗効果を極めて効果的に発揮させることができる。さらに、各抽出物毎にその抽出物の物性に対応させた顆粒となっていることから、異なった成分の混合による物性の劣化を回避することができ、プロポリス組成物が吸湿すること等により固結するのを効果的に防止することができるうえ、各抽出物中の油溶成分が混合時又は保存時に分離する等の問題も効果的に防止することができる。従って、３種類の抽出物をそれぞれ顆粒として組合わせることによって、極めて高い品質のプロポリス組成物顆粒製剤を提供することができる。

【００５２】・　超臨界抽出物を顆粒とする場合、予め超臨界抽出物１に対して重量比で付着防止剤を０．０１～２配合することにより容易に製造することができる。特に、付着防止剤としてカルシウムを用いることによって、ペースト状又は乳化液状の超臨界抽出物を粉末化す

る工程において、超臨界抽出物中の油分の分離や、粉末同士の付着による固結の発生を効果的に防止することができる。

【００５３】加えて、前記３種類の抽出物の顆粒をそれぞれコーティング顆粒とすることによって、各抽出物の体内への分散時期及び吸収時期を任意にコントロールすることが可能である。このため、３種類の抽出物の体内への吸収をより一層促進することができるとともに、３種類の抽出物による抗炎症作用の相乗効果を顕著に高めることができる。特に、親水性有機溶媒抽出物、水抽出物及び超臨界抽出物のコーティング顆粒のコーティング比を、それぞれ０．２～０．４、０．４～０．６及び０．０５～０．２となるように構成することによって、前記各抽出物の体内への吸収及び相乗効果を著しく顕著に高めることができる。

【００５４】すなわち、各抽出物の吸収面においては、親水性有機溶媒抽出物は疎水性であるため、胃での分散及び溶解がされ難いことから腸内での吸収は遅くなる傾向がある。水抽出物は、胃で極めて迅速に溶解及び分散されることから、腸管内に移行したときには消化液により大幅に希釈された状態となっており、腸管内での吸収が濃度依存的に行われることから、その吸収率は低い傾向にあった。このように、３種類の抽出物の吸収時期が揃わない場合には、充分な相乗効果を発揮することができずに各抽出物単独又は２種類の抽出物の相加的効果が発揮されるに止まってしまう可能性が高かった。しかしながら、前記コーティング比でコーティングされた３種類の抽出物のコーティング顆粒を含有するプロポリス組成物顆粒製剤では、体内への吸収時期を適切にコントロールすることができることから、各抽出物の吸収時期を揃えてそれらの相乗効果を発揮させやすくすることが可能となる。

【００５５】

【実施例】以下、前記実施形態を具体化した実施例及び比較例について説明する。

（比較例１）ブラジル産プロポリス原塊６ｋｇを粉砕機（（株）石崎電機製作所製のこなどん）で粉砕した後、９５容量％エタノール３０リットルを加えて室温で２４時間撹拌抽出した。次に、前記プロポリス粉砕物を含む抽出液を濾紙（アドバンテック東洋（株）製のＮｏ．２）で濾過して残渣を除去することによって、プロポリスのエタノール抽出液２７ｋｇ（固形分８．９重量％）を得た。得られた抽出液をエバポレーターにて２０重量％になるまで減圧濃縮し、エタノール抽出液１２ｋｇを得た。さらにこのエタノール抽出液３ｋｇを減圧で濃縮乾固してエタノール抽出物６００gを得た。このエタノール抽出物を乳鉢で粉砕することによってエタノール抽出物粉末とした。

【００５６】（比較例２）比較例１で得られたエタノール抽出後のプロポリス残渣を固形分換算で２ｋｇ計量し、水２０リットルを加えて４５℃で５時間撹拌抽出した。次に、前記プロポリス残渣を含む抽出液を粗濾過用布（ポリエステル生糸織物）にて残渣の水気がなくなるまで粗濾過して粗濾過液１９．０ｋｇを得た。この粗濾過液に珪藻土（中央シリカ（株）製のシリカ１００Ｆ）３４０ｇを加えて撹拌した後、濾紙（アドバンテック東洋（株）製のＮｏ．２）を用いて再度濾過することによって濾過液１８．７ｋｇを得た。この濾過液をエバポレーターにて２０重量％になるまで減圧濃縮し、水抽出液１．１ｋｇを得た。この水抽出液０．６ｋｇを凍結真空乾燥機を用いて凍結乾燥した。得られた凍結乾燥物を粉砕することによって水抽出物粉末１２０ｇを得た。

【００５７】（比較例３）比較例１で得られたエタノール抽出後のプロポリス残渣を固形分換算で１ｋｇ計量し、超臨界流体処理装置（三菱化工機（株）製）で２時間超臨界流体処理を行った。なおこのとき、超臨界ガスとして二酸化炭素を用い、流量５ｋｇ／時間、最高圧力３４５気圧（３５．０ＭＰａ）、温度４０℃の条件で抽出した。抽出物を均一に混合することによって超臨界抽出物５９．３ｇが得られた。

【００５８】（比較例４）ブラジル産プロポリス原塊２ｋｇを粉砕機（こなどん）で粉砕した後、水２０リットルを加えて４５℃で５時間撹拌抽出した。次に、前記プロポリス粉砕物を含む抽出液を粗濾過用布（ポリエステル生糸織物）にて残渣の水気がなくなるまで粗濾過して粗濾過液１７．０ｋｇを得た。この粗濾過液に珪藻土（中央シリカ（株）製のシリカ１００Ｆ）３４０ｇを加えて撹拌した後、濾紙（アドバンテック東洋（株）製のＮｏ．２）を用いて再度濾過することによって濾過液１６．５ｋｇを得た。この濾過液をエバポレーターにて２０重量％になるまで減圧濃縮し、水抽出液１．４ｋｇを得た。この水抽出液０．７ｋｇを凍結真空乾燥機を用いて凍結乾燥した。得られた凍結乾燥物を粉砕することによって水抽出物粉末１４０ｇを得た。

【００５９】（比較例５）ブラジル産プロポリス原塊１ｋｇを粉砕機（こなどん）で粉砕した後、超臨界流体処理装置（三菱化工機（株）製）で２時間超臨界流体処理を行った。なおこのとき、超臨界ガスとして二酸化炭素を用い、流量５ｋｇ／時間、最高圧力３４５気圧（３５．０ＭＰａ）、温度４０℃の条件で抽出した。抽出物を均一に混合することによって超臨界抽出物９８．３ｇが得られた。

【００６０】（実施例１）比較例１で得られたエタノール抽出物粉末１０．７ｇと、比較例２で得られた水抽出物粉末１．３ｇと、比較例３で得られた超臨界抽出物１．０ｇとを混合しプロポリス組成物１３．０ｇを得た。

【００６１】（実施例２）比較例１で得られたエタノール抽出物粉末１２．０ｇと、比較例２で得られた水抽出物粉末４．５ｇと、比較例３で得られた超臨界抽出物

１．０ｇとを混合しプロポリス組成物１７．５ｇを得た。

【００６２】（実施例３）比較例１で得られたエタノール抽出物粉末１７．０ｇと、比較例２で得られた水抽出物粉末３．０ｇと、比較例３で得られた超臨界抽出物１．０ｇとを混合しプロポリス組成物２１．０ｇを得た。

【００６３】（実施例４）比較例１で得られたエタノール抽出物粉末５．０ｇと、比較例２で得られた水抽出物粉末３．０ｇと、比較例３で得られた超臨界抽出物１．０ｇとを混合しプロポリス組成物９．０ｇを得た。

【００６４】（実施例５）比較例１で得られたエタノール抽出物粉末１０．７ｇと、比較例４で得られた水抽出物粉末１．３ｇと、比較例５で得られた超臨界抽出物１．０ｇとを混合しプロポリス組成物１３．０ｇを得た。

【００６５】（実施例６）比較例１で得られたエタノール抽出物粉末１２．０ｇと、比較例４で得られた水抽出物粉末４．５ｇと、比較例５で得られた超臨界抽出物１．０ｇとを混合しプロポリス組成物１７．５ｇを得た。

【００６６】＜ラジカル捕捉能試験＞健康食品製剤及び美容製剤として重要な生理活性作用である活性酸素消去作用をラジカル捕捉能試験によって比較した。

【００６７】比較例１～５及び実施例１～６の各組成物を無水エタノール中に各々０．００１重量％の濃度で溶解させた試料溶液を調製した。各試料溶液２ｍｌに、６０μＭのＤＰＰＨ（1,1-diphenyl-2-picrylhydrazyl）無水エタノール溶液２ｍｌを加えて混合し、ＤＰＰＨエタノール試料溶液を調製した後、室温で２０分間反応させた。その後、分光光度計（PERKIN ELMER UV Spectrometer Lambda４０）を用いて、各ＤＰＰＨエタノール試料溶液の波長５１７ｎｍにおける吸光度を測定した。また、対照として水を用いて同操作を行った後、そのときの吸光度を１００％として各ＤＰＰＨエタノール試料溶液の紫色除去能力（ラジカル捕捉率（％））を計算した。なお、このラジカル捕捉率の値が高いほど抗酸化活性が高いことを示している。結果を表１に示す。

【００６８】

【表１】

検体名	含有量（％）			ﾗｼﾞｶﾙ捕捉率（％）	阻害濃度 IC_{50}（重量％）	白血球貪食率（％）
	ｴﾀﾉｰﾙ抽出	水抽出	超臨界抽出			
比較例１	100	—	—	35.6	0.0030	120.2
比較例２	—	100	—	24.2	0.0029	125.5
比較例３	—	—	100	26.8	0.0033	120.0
比較例４	—	100	—	20.5	0.0030	—
比較例５	—	—	100	23.8	0.0035	—
実施例１	82.3	10.0	7.7	60.5	0.0010	163.9
実施例２	68.6	25.7	5.7	52.3	0.0012	154.2
実施例３	81.0	14.3	4.7	53.1	0.0011	155.3
実施例４	55.6	33.3	11.1	40.2	0.0015	135.8
実施例５	82.3	10.0	7.7	48.0	0.0015	—
実施例６	68.6	25.7	5.7	46.4	0.0015	—

その結果、３種類の抽出物を含有する実施例１～６のプロポリス組成物は、比較例１～５の組成物と比較して、抗酸化活性が顕著に高いことが確認された。特に、実施例１～３のプロポリス組成物の活性酸素消去作用は、実施例４～６と比較してより高いことが確認された。

【００６９】＜ヒアルロニダーゼ阻害活性試験＞アレルギー発現の機作の一つであるヒアルロニダーゼ作用を阻害する活性の強さを測定比較することで、抗アレルギー作用を比較した。

【００７０】比較例１～５及び実施例１～６の各組成物を、０．１Ｍ酢酸緩衝液（ｐＨ３．５）に各々０．００１～０．１重量％の各種濃度で溶解させた試料溶液を調製した。次に、予めヒアルロニダーゼを０．１２５ｍｌ（１１００ユニット（Ｕ））ずつ分注し、３７℃で２０分間保温しておいた溶液中に前記各試料溶液を加え、さらに３７℃で２０分間加温して反応させた。続いて、ヒアルロン酸カリウム（１．５ｍｇ／ｍｌ）を含む酢酸緩衝液を加えて３７℃で４０分間反応させた。反応停止後に発色させ、各試料（サンプル）の５８５ｎｍにおける吸光度を測定し、ヒアルロニダーゼ活性阻害率（％）を下記数１の算出式により求めた。また、対照として０．１Ｍ酢酸緩衝液を用いて同操作を行い、コントロールとした。

【００７１】

【数１】

$$\text{阻害率} = \frac{(\text{コントロールの吸光度}) - (\text{サンプルの吸光度})}{(\text{コントロールの吸光度})} \times 100$$

さらに、前記各種濃度の試料溶液で算出されたヒアルロニダーゼ活性阻害率の値を用いて、コントロールのヒアルロニダーゼ活性を５０％阻害する濃度 IC_{50}（重量％）を求めた。結果を上記表１に示す。その結果、３種

類の抽出物を含有する実施例１～６のプロポリス組成物は、比較例１～５の組成物と比較して、ヒアルロニダーゼに対して著しく高い阻害効果を有していることが確認された。特に、実施例１～３のプロポリス組成物は、実施例４～６と比較してより高い効果があることが確認された。

【００７２】＜白血球貪食能試験＞免疫賦活作用の指標として白血球貪食能を検討するために、死滅したイースト菌に対するラット白血球の貪食能促進効果について試験を行った。試料としては、比較例１～３及び実施例１～４の組成物をそれぞれ１１０μｇ／ｍｌの濃度になるようにジメチルスルフォキシド（ＤＭＳＯ）に溶解させた試料溶液を使用した。また、陽性対照としてクレスチン粉末（三共製薬（株）製）を用いて同様に対照試料溶液を調製した。

【００７３】まず、Wistar系ラット（体重２２０ｇ前後）の腹腔中にグリコーゲンを投与した。４時間後にラットを脱血到死させ、生理食塩水を腹腔内に注入して腹腔内を洗浄した後、腹腔内に存在する白血球とともに前記洗浄液を回収した。この洗浄液をリン酸緩衝液（ＰＢＳ）で２回洗浄し、セルカウントを行った後、５×１０⁶個／ｍｌの細胞濃度となるように細胞浮遊液を調製した。また、予めイースト死滅菌液YEAST(Bakers yeast)TypeII（SIGMA社製）を０．２容量％になるようにＰＢＳ中に懸濁させた後にラット血清０．１ｍｌを加え、１２１℃で１５分間オートクレーブ殺菌処理することによってイースト死滅菌溶液を調製した。

【００７４】次に、前記細胞浮遊液０．２ｍｌに各試料溶液を０．０４ｍｌ加え、室温で１０分間インキュベートした各反応液に、前記イースト死滅菌溶液０．１ｍｌを加えて３７℃で３０分間インキュベートした。冷却後、９５容量％エタノールに塩基性フクシンを１重量％になるように溶解し、０．４５μｍのフィルターで濾過することにより調製したフクシン染色液を０．０５ｍｌ加えて染色した。また、対照としてはＰＢＳを用いて同操作を行った。最後に、前記フクシン染色液で染色されなかった細胞数（イースト菌を貪食しなかった白血球数）及びフクシン染色液で染色された細胞数（イースト菌を貪食した白血球数）をカウントし、白血球貪食率（％）すなわち全細胞数に対するイースト菌を貪食した細胞数の割合を求めた。結果を上記表１に示す。

【００７５】その結果、３種類の抽出物を含有する実施例１～４のプロポリス組成物は、比較例１～３の組成物と比較して、高い白血球貪食作用が発揮され、免疫賦活作用が確認された。特に、実施例１～３のプロポリス組成物の白血球貪食能は極めて高いことが確認された。なお、陽性対照としてのクレスチン粉末の白血球貪食率は１５０．４％であった。

【００７６】（実施例７）遠心流動型コーティング造粒装置（フロイント産業（株）製）を用い、回転数２００r.p.m.、８０℃の条件下で、精製白糖及びトウモロコシデンプンからなる原料顆粒（ノンパレル－１０１：商標登録）１００ｇに、比較例１のエタノール抽出液２５０ｇをドライエアーで乾燥しながら徐々に噴霧した。同時にコーンスターチ２１０ｇを徐々に添加し、前記原料顆粒表面にエタノール抽出物及びコーンスターチを付着させたエタノール抽出物顆粒２９９ｇを得た。

【００７７】また、同条件にて、同原料顆粒１００ｇに、比較例２の水抽出液６７．５ｇを品温が５０℃を越えないように、ドライエアーで乾燥しながら徐々に噴霧した。同時にコーンスターチ１２．５ｇを徐々に添加し、原料顆粒表面に水抽出物及びコーンスターチを付着させた水抽出物顆粒１１３．５ｇを得た。また、回転数１８０r.p.m.、室温下で原料顆粒１００ｇに、６０重量％のコーンスターチ懸濁液３７．５ｇを噴霧しながら、予め１７重量％含有粉末とした比較例３の超臨界抽出物７５ｇ及びコーンスターチ５７．５ｇを徐々に添加し、乾燥して、超臨界抽出物顆粒２２３．５ｇを得た。

【００７８】なお、前記超臨界抽出物の粉末化は以下のように行った。比較例３の超臨界抽出物２５ｇに卵殻カルシウムを２０ｇ混合し、さらにパインフロー５５ｇを混合して粉末とした後、５０ｇのコーンスターチを混合し１７重量％含有超臨界抽出物粉末１５０ｇを作製した。最後に、前記エタノール抽出物顆粒７７．０ｇ（エタノール抽出物として１０．７ｇ相当）と、水抽出物顆粒１２．１ｇ（水抽出物として１．３ｇ相当）と、超臨界抽出物顆粒２０ｇ（超臨界抽出物として１ｇ相当）とを混合してプロポリス組成物顆粒製剤とした。

【００７９】（実施例８）実施例７のエタノール抽出物顆粒７５ｇに、コーティング剤としてコーンスターチ３２．１５ｇを添加（コーティング）し、エタノール抽出物のコーティング顆粒１０７．１５ｇを得た。なお、この顆粒のコーティング比は０．３である。また、実施例７の水抽出物顆粒５０ｇに、コーティング剤としてコーンスターチ５０ｇを添加し、水抽出物のコーティング顆粒１００ｇ（コーティング比は０．５）を得た。また、実施例７の超臨界抽出物顆粒１００ｇに、コーティング剤としてコーンスターチ１１．２ｇを添加し、超臨界抽出物のコーティング顆粒１１１．２ｇ（コーティング比は０．１０）を得た。最後に、前記エタノール抽出物のコーティング顆粒１１０．２ｇ（エタノール抽出物として１０．７ｇ相当）と、水抽出物のコーティング顆粒２４．１ｇ（水抽出物として１．３ｇ相当）と、超臨界抽出物のコーティング顆粒２２．２ｇ（超臨界抽出物として１ｇ相当）とを混合してプロポリス組成物顆粒製剤とした。

【００８０】＜浮腫抑制試験＞抗炎症作用の指標となる浮腫抑制作用を検討するために急性炎症モデルラットを作製し、その炎症抑制効果について試験を行った。まず、Wistar系ラット（体重２２０ｇ前後）を一日絶食さ

せ、右後股足蹠に１重量％カラゲニン溶液０．１ｍｌを皮下注射し、４時間後に足の体積を測定した。試料としては、比較例１～３、実施例１～４、実施例７及び実施例８の各組成物を１０％アラビアゴム溶液中に溶解させ、プロポリス（抽出物）濃度が２０ｍｇ／ｍｌになるように調整した。各試料溶液をカラゲニン投与の１時間前、３時間前又は５時間前に、それぞれ２００ｍｇ／ｋｇ／１０ｍｌになるように経口投与した。また、対照としては滅菌水を用いた。そして、ラットの足の体積の測定結果からカラゲニン浮腫抑制率（％）を求めた。結果を表２に示す。

【００８１】

【表２】

検体名	カラゲニン浮腫抑制率（％）			
	１時間前投与	３時間前投与	５時間前投与	平均
比較例１	３．４	３８．２	３０．２	２３．９
比較例２	２５．０	１０．２	９．０	１４．７
比較例３	５．３	４４．２	１５．６	２１．７
実施例１	４．３	６９．０	４０．２	３７．８
実施例２	１３．２	５５．７	３３．６	３４．１
実施例３	８．５	６３．４	３８．３	３６．７
実施例４	１５．６	４０．５	２９．１	２８．４
実施例７	４．７	６７．４	４０．２	３７．４
実施例８	３．４	６６．３	５０．８	４０．２

その結果、３種類の抽出物を含有する実施例１～４、実施例７及び実施例８のプロポリス組成物顆粒製剤は、比較例１～３の組成物と比較して、カラゲニン投与３時間前に投与した群において、急性炎症による浮腫に対して著しく高い抑制効果が確認された。各抽出物（比較例１～３の組成物）はそれぞれ抗炎症作用（浮腫抑制作用）を発揮するが、３種類の抽出物を混合したプロポリス組成物（実施例１～４、実施例７及び実施例８）は相乗的に高められた抗炎症効果を発揮することが確認された。さらに、エタノール抽出物の混合比率を高めることによりフラボノイド類の含有量を増大させるとともに、補助的に水抽出物に含まれる有機酸類及び多糖類と超臨界抽出物に含まれる疎水性の高い物質（油脂成分等）とが加わることにより、抗炎症作用をより一層顕著に高めることができる。

【００８２】一方、実施例８のプロポリス組成物顆粒製剤は、実施例７の顆粒製剤よりも高い抑制効果が確認された。この現象は、エタノール抽出物顆粒及び超臨界抽出物顆粒がコーティングされることより、それらに含まれる有効成分の胃酸への接触が抑制されて凝集が防止され、腸内で分散されるようになって吸収量が著しく増加したことによるものと推測される。さらに、水抽出物顆粒のコーティング比を増加させて分散時期を遅らせることにより、その有効成分がエタノール抽出物及び超臨界抽出物の吸収時期とほぼ同時期に吸収されるようになり、３種類の抽出物中の有効成分の吸収時期が揃うとともに吸収量が増大したことによるものと推測される。従って、３種類の抽出物中の有効成分による相乗効果が極めて顕著に発揮されたことによるものと予想される。

【００８３】なお、上記各実施形態は、次のように変更して具体化することも可能である。

・　プロポリス原塊を用いて先に親水性有機溶媒抽出を行った後、その残分を水抽出し、さらにその残分を超臨界抽出するように構成すること。或いは、プロポリス原塊を用いて先に親水性有機溶媒抽出を行った後、その残分を超臨界抽出し、さらにその残分を水抽出するように構成すること。このように構成した場合、原料費節減効果をさらに効果的に発揮させることができる。

【００８４】さらに、前記実施形態より把握できる技術的思想について以下に記載する。

・　前記親水性有機溶媒抽出プロポリス、水抽出プロポリス及び超臨界抽出プロポリスの配合割合を、重量比で２～１５：０．６～５：１としたことを特徴とする請求項１から請求項４のいずれかに記載のプロポリス組成物。

【００８５】・　前記親水性有機溶媒抽出プロポリスの顆粒をコーティング比０．２～０．４のコーティング顆粒とし、前記水抽出プロポリスの顆粒をコーティング比０．４～０．６のコーティング顆粒とするとともに、前記超臨界抽出プロポリスの顆粒をコーティング比０．０５～０．２のコーティング顆粒とすることを特徴とする請求項５に記載のプロポリス組成物顆粒製剤。但し、前記コーティング比は、コーティング顆粒重量に対するコーティング剤重量の割合を示す。

【００８６】・　前記超臨界抽出プロポリスの顆粒は、超臨界抽出プロポリス１に対して付着防止剤を重量比で０．０１～２配合して粉末化したものであることを特徴とする請求項５に記載のプロポリス組成物顆粒製剤。

【００８７】・　請求項１から請求項４のいずれかに記載のプロポリス組成物を含有することを特徴とする健康食品製剤。このように構成した場合、健康食品及び化粧品として高い効能を発揮することができる健康食品製剤を効率良く安価に提供することができる。

【００８８】・　請求項１から請求項４のいずれかに記

載のプロポリス組成物を含有することを特徴とする美容製剤。このように構成した場合、健康食品及び化粧品として高い効能を発揮することができる美容製剤を効率良く安価に提供することができる。

【００８９】・　請求項５に記載のプロポリス組成物顆粒を含有することを特徴とする健康食品製剤。このように構成した場合、健康食品及び化粧品として高い効能を発揮することができるとともに、安定性に優れた健康食品を提供することができる。

【００９０】・　親水性有機溶媒抽出プロポリスと、水抽出プロポリスと、超臨界抽出プロポリスとを含有するプロポリス組成物であって、前記水抽出プロポリス及び超臨界抽出プロポリスから選ばれる少なくとも１種は、プロポリス原塊を親水性有機溶媒で抽出した後の残渣より抽出されたものであることを特徴とするプロポリス組成物。このように構成した場合、健康食品及び化粧品素材として高い効能を発揮することができる。

【００９１】

【発明の効果】以上詳述したように、この発明によれば、次のような効果を奏する。請求項１から請求項４に記載の発明のプロポリス組成物、並びに請求項５に記載のプロポリス組成物顆粒製剤によれば、健康食品及び化粧品素材として高い効能を発揮することができる。

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(72)発明者　山田　英生
岡山県苫田郡鏡野町市場194番地　株式会社山田養蜂場内
(72)発明者　徳永　勝彦
岐阜市加納桜田町１丁目１番地　アピ　株式会社内
(72)発明者　丸山　広恵
岐阜市加納桜田町１丁目１番地　アピ　株式会社内
(72)発明者　坂本　貴
岐阜市加納桜田町１丁目１番地　アピ　株式会社内
(72)発明者　三島　敏
岐阜市加納桜田町１丁目１番地　アピ　株式会社内

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